Polymyalgia rheumatica in primary care: an exploration of the challenges of diagnosis and management using survey and qualitative methods

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Declaration

My interest in PMR began whilst working in elderly care as a junior doctor. During my GP vocational training I undertook a Masters in medical science degree culminating in a dissertation, investigating PMR using a consultation database based at Keele University. My research training has been funded through a National Institute of Health Research In-Practice Fellowship and NIHR School of Primary Care Research GP progression fellowship.

This thesis is part of the wider inflammatory rheumatology program with the initial research idea and Ph.D. proposal being developed by Professor Christian Mallen. The subsequent Ph.D. development, ethical approval, data gathering, interpretation of findings and conclusions are my own. The running of the two studies related to this thesis has been supported by my supervisors who also provided advice on writing the thesis. Additionally the wider administrative team linked to the inflammatory program at the Research Institute of Primary Care and Health Sciences at Keele University provided support throughout the study period.

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Abstract

Background: Polymyalgia rheumatica (PMR) is one of the most common inflammatory arthritic disorders seen in older people and is closely related to giant cell arteritis (GCA). Most PMR patients are diagnosed and managed in general practice yet primary care focused research is lacking.

Methods: Three complimentary studies were undertaken to investigate PMR and GCA in primary care.

1. A systematic review investigating the diagnosis and diagnostic criteria for PMR
2. A national questionnaire survey of 5000 randomly selected general practitioners (GPs)
3. Qualitative telephone interview study of GPs.

Results: No validated diagnostic criteria or combination of investigations were identified that could be used for definitive PMR diagnosis. 1249 (25%) GPs responded to the questionnaire survey. 24 GPs were interviewed for the qualitative study. Features used by GPs to identify PMR were largely in-line with current guidance. Diagnosis was found to be challenging with GPs relying heavily on response to treatment with glucocorticoids. Guideline advised investigations were not routinely requested. Concerns surrounding long term treatment with glucocorticoids were widespread in relation to both potential adverse effects and on-going monitoring.

Headache was the main symptom used to identify potential patients with GCA. Other symptoms indicative of GCA were less frequently used. Significant fears relating to missing a diagnosis of GCA exist as well as frustrations in forward treatment and

investigation of potential GCA patients with clear regional variations in assessment and referral pathways.

Conclusion: For PMR, focused GP educational strategies are needed to promote the need to exclude relevant differential diagnoses and on-going vigilance for treatment complications. Raising awareness of the range of potential features that GCA can present with could aid and improve diagnosis. To complement this, a national standard for fast track pathways for suspected GCA patients to relevant expertise could help to improve care and outcomes for patients with GCA.

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"There is, perhaps, no disease as to which professional opinion differs more than as to rheumatic gout. This diversity of views is unfortunate, as it affects the kind of treatment and mode of life of the patient, and it disturbs the lay mind and gives occasion for remarks as to the uncertainties of medicine."

William Bruce 1888 p811

Chapter 1: The history and epidemiology of polymyalgia rheumatica

1.1 Introduction

This thesis is concerned with polymyalgia rheumatica (PMR), and the attitudes and beliefs that general practitioners (GPs) have towards its diagnosis and management**.** In this chapter, the content of the thesis will be introduced with a specific focus on the central disease being studied: polymyalgia rheumatica. Specific areas that will be covered include an introduction to PMR, the history of PMR, PMR in general practice and the epidemiology of PMR.

1.2 Introduction to the disease polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is a relatively common inflammatory rheumatic condition that affects older people. [Michet and Matteson 2008] It is estimated that over 700,000 Americans live with the condition. [Lawrence et al 2008] Patients presenting with PMR are typically over 60 years of age [Smeeth et al 2006] and classically suffer with bilateral shoulder and/or hip girdle pain, morning stiffness and muscle aches, although the presenting features can be non-specific and vary widely. [Dasgupta et al 2008] Patients with PMR commonly have elevated inflammatory markers (including the erythrocyte sedimentation rate (ESR), C Reactive Protein (CRP), plasma viscosity (PV) or fibrinogen [Dasgupta et al 2010, McCarthy et al 2013]). Typically, patients with PMR respond rapidly to treatment with low dose glucocorticoids (e.g. 15mg of prednisolone daily). [Dasgupta et al 2010] No diagnostic test exists for PMR, therefore diagnosis can be challenging in view of the non-specific nature of the presentation of PMR and because of a wide range

of differential diagnoses which also respond to low dose glucocorticoids and can present in a similar way. The differential diagnosis of PMR is discussed in more detail later in this chapter.

PMR is closely associated with giant cell arteritis (GCA). Around 1 in 5 patients with PMR develop GCA during their illness and between 40 and 60% of patients with GCA report symptoms of PMR. [Salvarani et al 2008] GCA is the most common large vessel vasculitis with over a quarter of a million Americans living with the disease. [Lawrence et al 2008] The features of GCA are caused by inflammation, predominantly of the branches of the external carotid artery, ciliary artery and retinal arteries. [Barraclough et al 2012] If treatment is delayed, GCA can potentially lead to irreversible blindness. Because of this intimate overlap between PMR and GCA, practitioners treating PMR have to be vigilant to the possibility of co-existing GCA. It is also important to discuss and investigate GCA when researching PMR. This thesis will therefore address issues surrounding the diagnosis and management of GCA as a secondary research question.

In the United Kingdom PMR is a condition which is diagnosed and managed predominantly in primary care [Barraclough et al 2008, Helliwell et al 2013] yet there has been limited research undertaken in this setting. Given the paucity of research in this setting, this thesis has been undertaken to investigate the diagnosis and management of PMR in a primary care setting. The following sections describe the history of PMR (Section 1.3), the epidemiology of PMR (section 1.4) and PMR in a primary care context (Section 1.5). Section 1.6 focuses on GCA.

1.3 The History of PMR

William Bruce in his article entitled "Senile Rheumatic Gout" published in the BMJ in 1888 is often attributed with publishing the first description of what we now consider to be polymyalgia rheumatica. In this paper he notes that:

"There is, perhaps, no disease as to which professional opinion differs more than as to rheumatic gout. This diversity of views is unfortunate, as it affects the kind of treatment and mode of life of the patient, and it disturbs the lay mind and gives occasion for remarks as to the uncertainties of medicine." **Bruce 1888 p811**

In this seminal work on polymyalgia rheumatica, he described five cases that appeared to be distinct from rheumatoid arthritis and gout. [Bruce 1888] All five cases however were male and, as we know now, polymyalgia rheumatica tends to affect women more than men.

In post Second World War Europe, several case series of potential polymyalgia rheumatica patients that were published, with different terms for PMR being coined. These included descriptors such as periarthrosis humeroscapularis and peri-extra-articular rheumatism. [Hunder 2006]

Barber (1957) has been attributed as being the first person to use the term "polymyalgia rheumatica." His case series entitled "*Myalgic syndrome with constitutional effects: polymyalgia rheumatica*" was published in the Annals of Rheumatic Diseases in 1957. [Barber 1957] This article identified morning stiffness as one of the cardinal features of PMR. It also identified other features which have been shown to be consistently

associated with PMR. These include anaemia, raised erythrocyte sedimentation rate (ESR), and bilateral shoulder and hip girdle pain and/or discomfort, which are now widely accepted as symptoms typical of PMR. Most case series agree that given time, patients would eventually improve. Barber however noted the rapid response demonstrated by patients who were given cortisone treatment.

"*no doubt of their immediate response to corticosteroids*" **Barber 1957 p231**

Barber also recognised the quite significant impacts that PMR could have on patient's everyday life saying,

"*The somewhat melodramatic description of their pain by these patients tends to suggest a diagnosis of psychoneurosis until the E.S.R. has been measured.*"

Barber 1957 p232

Barber also advised that the diagnosis be based largely on negative findings (i.e. the absence of joint involvement, muscle weakness or atrophy, after a lengthy period of observation). Barber's case series of 12 patients included 2 men and 10 women. [Barber 1957]

Gordon (1960) in the Quarterly Journal of Medicine confirmed Barber's finding in relation to corticosteroid treatment noting that:

"*In every case, if an adequate dose was given, a remarkable and rapid remission of symptoms was induced within 48 hours."* **Gordon 1960 p482**

This paper also highlighted that all pain and stiffness had completely or almost completely disappeared with treatment. [Gordon 1960]

Boyle was the first to advocate the use of low dose glucocorticoids for the treatment of PMR. [Boyle and Beatty 1961]

> "*Six patients had symptoms severe enough to warrant a trial of steroids, and all of them made a good response to prednisone in doses of 15 mg per day or less. Once again, however, there was a prompt relapse of symptoms if the drug was withdrawn"* **Boyle 1961 p22**

An editorial written in the BMJ in December of 1957 further highlighted that patients with PMR tended to be middle or old age women and highlighted the controversies and difficulties in diagnosing PMR in view of its lack of clear physical signs or symptoms adding that:

> "*often the patients' symptoms were wrongly attributed to psychogenic causes"*
>
> **BMJ 1957 (editorial) p1483**

Bruce's case series of PMR patient was described over 125 years ago but sadly, much of the original writing of Bruce, particularly the 'diversity of views' still holds true today. ESR remains the predominant investigation used to help diagnose patients, glucocorticoids remain the mainstay of treatment and it still causes significant impacts on patients' lives both prior to diagnosis and during treatment.

1.4 The epidemiology of PMR

1.4.1 Introduction and methods used to investigate the epidemiology of PMR

The incidence of PMR (number of new cases per population at risk in a given time period) varies geographically, and with age. PMR is rare in patients under the age of 50. [Smeeth 2006] The epidemiological study of PMR is challenging, as it is difficult to determine and compare incidence and prevalence (proportion of the population having the condition) rates between geographical regions, as standardised methodologies and uniform diagnostic classification criteria are not widely used. There is currently no gold standard diagnostic test for PMR, however, classification criteria that conform to the American College of Rheumatology (ACR) standards have now been developed for use in future research. [Dasgupta et al 2012] This section reviews the literature concerning the epidemiology of PMR and was undertaken as part of the initial phases of the PhD in November 2011.

In order to identify relevant evidence on the epidemiology of PMR, a literature search of Medline and EMBASE was undertaken using the thesaurus explode function and the search terms polymyalgia rheumatica, epidemiology, incidence and prevalence. Titles and abstracts were screened and the reference lists from identified citations reviewed for other additional publications that were potentially relevant.

The majority of the studies identified related to the incidence of PMR and the findings of these incidence studies are summarised in Table 1.1. The identified studies were usually undertaken in North America or Europe and are described in more detail the following sections.

Table 1.1 Summary of the epidemiology of polymyalgia rheumatica

Reference	Setting	Study Type	Population	Inclusion Criteria	Female: Male Ratio	Epidemiological results	
Chuang 1982	Minnesota, USA	Prospective observational study	n=96	Chuang/Hunder classification criteria	1.7:1	**Age Group (years)**	**Incidence (per 100,000 patient years)**
						0-49	0.1
						50-59	19.8
						60-69	48.1
						70-79	112.2
						80+	86.2
						All ages	11.1
Doran 2002	Minnesota, USA	Prospective observational study	n=378	Chuang/Hunder classification criteria	2:1	In patients over 50 years of age, incidence was 58.7 per 100,000 patient years	
Gonzalez-Gay 1999	Xeral Lugo Hospital, Spain	Retrospective observational study	n=185	Clinical records of patients diagnosed with PMR between January 1987 and December 1996 Excluded patients with conditions mimicking PMR Patients sub-grouped into total PMR (PMR patients including PMR with associated GCA) and isolated PMR (only PMR patients with no associated GCA)	Not given	Total PMR (PMR with associated GCA): 18.67 per 100,000 patient years Isolated PMR (no evidence of associated giant cell arteritis): 13.52 per 100,000 patient years	

Reference	Setting	Study Type	Population	Inclusion Criteria	Female: Male Ratio	Epidemiological results
Gran 1997	Aust Agder, Norway	Prospective observational study	n=322	All physicians suspecting PMR asked to refer patients to rheumatology. Bird[1] classification criteria used as inclusion criteria for study.	1.65:1	Incidence in the population of 50 years and above 112.6 per 100,000 patient years
Kyle 1985	Cambridge, UK	Cross sectional study	n=650	650 patients over the age of 65 invited to an interview to undertake a previously validated (specificity 97%) screening questionnaire[1] administered by interview. Positively identified patients were then assessed by a rheumatologist and included the study if the Jones/Hazelman criteria were achieved	Not given	Incidence in patients over the age of 65 years old 4/1000 patient years. (400 per 100,000 patient years)
Salvarani 1991	Reggio Imilia, Italy	Retrospective observational study	n=99	Persistent pain for more than one month involving two of the following: neck, shoulder or pelvic girdle EMS[b] for more than one hour Rapid response to prednisolone of less than 20mg per day Absence of other diseases which could mimic these symptoms	2:1	Incidence in patients over the age 50 years: 12.7 per 100,000 patient years

Reference	Setting	Study Type	Population	Inclusion Criteria	Female: Male Ratio	Epidemiological results	
Schaufelberger 1995	Goteburg, Sweden	Prospective observational study	n=220	Pain and stiffness affecting at least two groups of: neck, shoulders, upper arms, hips and thighs for two weeks Absence of inflammatory arthritis Elevated ESR[a] of more than 40 Age of 50 or more No evidence of: rheumatoid arthritis, systemic lupus erythematosis, periarteritis nodosa, infection or malignant disease.	2.49:1	Incidence in patients with PMR with negative temporal artery biopsy[2] was: 17 per 100,000 patient years Incidence in patients older than 50 with PMR with negative temporal artery biopsy[2] was: 50 per 100,000 patient years	
Smeeth 2006	UK General Practice Research Database (GPRD) UK	Retrospective observational study	n=15013	Older than 40 years of age First diagnosis of PMR entered into their general practice record 2 prescriptions for oral corticosteroids, one within six months of diagnosis and the two prescriptions being within six months of each other	2:1	**Age Group (years)** 40-49 50-59 60-69 70-79 80+ All ages	**Incidence (per 100,000 patient years)** 4.1 27 98 229 222 84

[a] ESR: erythrocyte sedimentation rate, [b]EMS: early morning stiffness

[1]1) Have you at any time had arthritis or rheumatism, 2) Do you have stiffness around the neck and both shoulder, 3) Do you wake up with stiffness or aching around your shoulder. Does this stiffness last for more than one hour 4) Do you wake up with stiffness or aching in your joints 5) Have you ever had any swelling in any joints 6) Symptoms of temporal arteritis: Scalp tenderness, Severe headaches, Visual loss.

Two prevalence studies were identified. A study conducted by Lawrence (2008), derived the prevalence of PMR using published data from small scale studies and the corresponding 2005 United States Census Bureau population estimates. They concluded that the number of people with PMR in the United States was 711,000. [Lawrence et al 2008] Salaffi (2005) in Marches, Italy conducted a cross-sectional study of 3664 patients. Patients identified with a possible musculoskeletal disorder were then formally assessed by a rheumatologist and diagnosed according to internationally accepted classification criteria (Bird classification criteria were used for PMR patients. [Bird et al 1979]) The study had a 58.8% response rate and the prevalence of PMR above the age of 50 years old was 0.7%. This was equivalent to rheumatoid arthritis in patients over 50 years old. [Salaffi et al 2005]

1.4.3 Age

Studies suggest that PMR is rare in patients under the age of 50. Smeeth (2006) found that the age adjusted incidence of PMR in the 40-49 year group was 4.1 per 100,000 patient years which compared to an age adjusted incidence of 229 per 100,000 patient years in the 70 to 79 year old group. [Smeeth et al 2006] Chuang (1982) described only one patient younger than 50 years of age (who was excluded from the main analysis in view of their age) resulting in an incidence of 0.1 per 100,000 patient years in people younger than 50. Those presenting with suspected PMR under the age of 50 years are often excluded from research studies as they may have atypical disease. The epidemiology of PMR in patients under the age of 50 has therefore not been widely studied. [Chuang et al 1982]

1.4.4 Incidence

The highest incidence rate reported in the identified studies was 112.6 per 100,000 patient years in patients aged over 50 years in Aust Agder, Southern Norway. [Gran and Myklebust 1997] By contrast the lowest reported incidence rate was found in Reggio Imilia, Northern Italy which had an incidence of 12.7 per 100,000 patient years in those aged over 50 years. [Salvarani et al 1991] Of particular note is the increasing incidence of PMR with increasing latitude. This has in part been attributed to genetic and environmental factors [Cimmino et al 1997], but may also be due to varying methodological approaches which will be discussed in more detail in Section 1.4.4.

Most relevant to this thesis however, is the paper published by Smeeth (2006) as it is a study focusing on the epidemiology of PMR in the UK. This study used one of the largest cohorts of patients diagnosed with PMR. Data were extracted from the General Practice Research Database (GPRD). This database consists of the electronic medical records of patients registered with contributing UK general practices and relied on the appropriate diagnostic code for PMR being used in the database to identify patients with PMR. Patients who were younger than 40 years old were excluded. One limitation of this dataset is uncertainty around the diagnostic accuracy and the lack of a standardised approach to diagnosis. Therefore, as a proxy to improve diagnostic accuracy, cases included in the analysis also had to have had two prescriptions for glucocorticoids, the first within 6 months of the diagnosis date and the second within six months of the first prescription being issued. The overall incidence of PMR was 8.42 per 10,000 person years with a female to male ratio of 2:1. As other epidemiological studies of PMR have also demonstrated, incidence rates increase sharply with increasing age such that the highest

incidence of PMR in this study was found in women in the 70 to 79-year-old group (22.9 per 10,000 patient years). [Smeeth et al 2006]

PMR occurs more frequently in women. The female to male ratio for patients with PMR varies between 1.65 to 1 to 2.49 to 1. [Gran and Myklebust 1997, Schaufelberger et al 1995]

1.4.4 Factors impacting on the epidemiological research of PMR

The published incidence of PMR ranges from a low of 12.7/100,000 patient years in Italy [Salvarani et al 1991] to a high of 112.6/100,000 patient years in Norway. [Gran and Myklebust 1997] This variation in incidence has led some researchers to hypothesise that PMR is linked to latitude. [Cimmino et al 2000] However, differences in incidence are also likely to reflect a lack of standardised recruitment methodologies and participant classification. Studies identified recruited patients predominately from secondary care settings [Gonzalez-Gay et al 1999], although an attempt was made by some to include primary care patients. [Gran and Myklebust 1997] Whilst the diagnostic accuracy in general practice has been questioned [Bahlas et al 2000], the recently published classification criteria highlight the challenges of diagnosing PMR in all settings. [Dasgupta et al 2012] Studies only including those from secondary care are likely to underestimate the true incidence of PMR, as patients with classical disease are seldom referred to specialist services [Barraclough et al 2008, Helliwell et al 2013] and will not be included in incidence estimates based on hospital studies. It is also a possibility that for some studies conducted in some regions of the world, the availability of high quality and accurate

primary care data may simply not be available and so secondary care data has to be relied upon to conduct such studies again resulting in lower overall incidence estimates. Conversely, primary care database studies, may result in over or under-estimates of incidence and or prevalence of PMR due to diagnostic inaccuracy. As such, the true population level burden associated with PMR is largely an estimate.

1.5 Polymyalgia rheumatica and primary care

1.5.1 Introduction

Primary care in the UK remains, for most patients, the first point of access to medical care. General practitioners (GPs) are defined by WONCA Europe (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians) as:

> "*specialist physicians trained in the principles of the discipline. They are personal doctors, primarily responsible for the provision of comprehensive and continuing care to every individual seeking medical care irrespective of age, sex and illness*. *In negotiating management plans with their patients they integrate physical, psychological, social, cultural and existential factors, utilising the knowledge and trust engendered by repeated contacts."*

[http://www.woncaeurope.org/sites/default/files/documents/Definition%203rd%20ed%202011%20with%20revised%20wonca%20tree.pdf. Accessed 7/12/2015]

GPs undertake over 90% of medical contacts in the UK National Health Service (NHS) and are therefore key to the early identification and on-going management of many chronic diseases. PMR and GCA are no exception to this, and as such GPs need to be aware of the possible diagnosis of PMR or GCA, given that they are likely to be the first clinicians to see patients presenting with these conditions. GPs are also well placed to provide follow up and continuing care and support for patients with PMR and GCA.

PMR can be challenging to diagnose, as early symptoms can be non-specific and there is currently no gold standard diagnostic test. Guidelines on the diagnosis and management of PMR were published by the British Society of Rheumatology and British Health Professionals in Rheumatology in 2010.[Dasgupta et al 2010] These guidelines, summarised in Figure 1.1, represent a significant step forward for clinicians, as no widely accepted guidelines describing diagnosis and management previously existed. The guidelines however, are largely based on secondary care expert opinion. This reflects the lack of research surrounding PMR and suggests difficulties in the integration of primary and secondary care for the management of rheumatological disorders. Expert opinion is often considered to be low quality evidence. [Greenhalgh 1997] Furthermore, expert consensus evidence is less likely to be relevant in a different healthcare setting where patients typically have a different range of symptoms and a different response to treatment.

Jordan (2010) reported that a general practitioner working full-time with a list size of approximately 2500 patients could expect to consult with five patients with PMR annually. [Jordan 2010] These findings relate to an average per general practitioner calculated from pooled consultation data obtained from twelve general practices and

assumes a practice size of 10,000 patients with four full time general practitioners. The data does not however, specify whether the encounter was a first encounter, new encounter or follow up encounter and compared to osteoarthritis (180 consultations annually) or gout (35 consultations annually) in the same study, the workload associated with PMR in primary care is relatively small. [Jordan 2010]

The frequency with which PMR is encountered by GPs will vary depending on the demographic of the practice population. However, based on the overall incidence rates given by Smeeth [Smeeth et al 2006] a full time GP can expect to see one or two new cases annually.

Figure 1.1. Summary of BSR/BHPR guidelines.

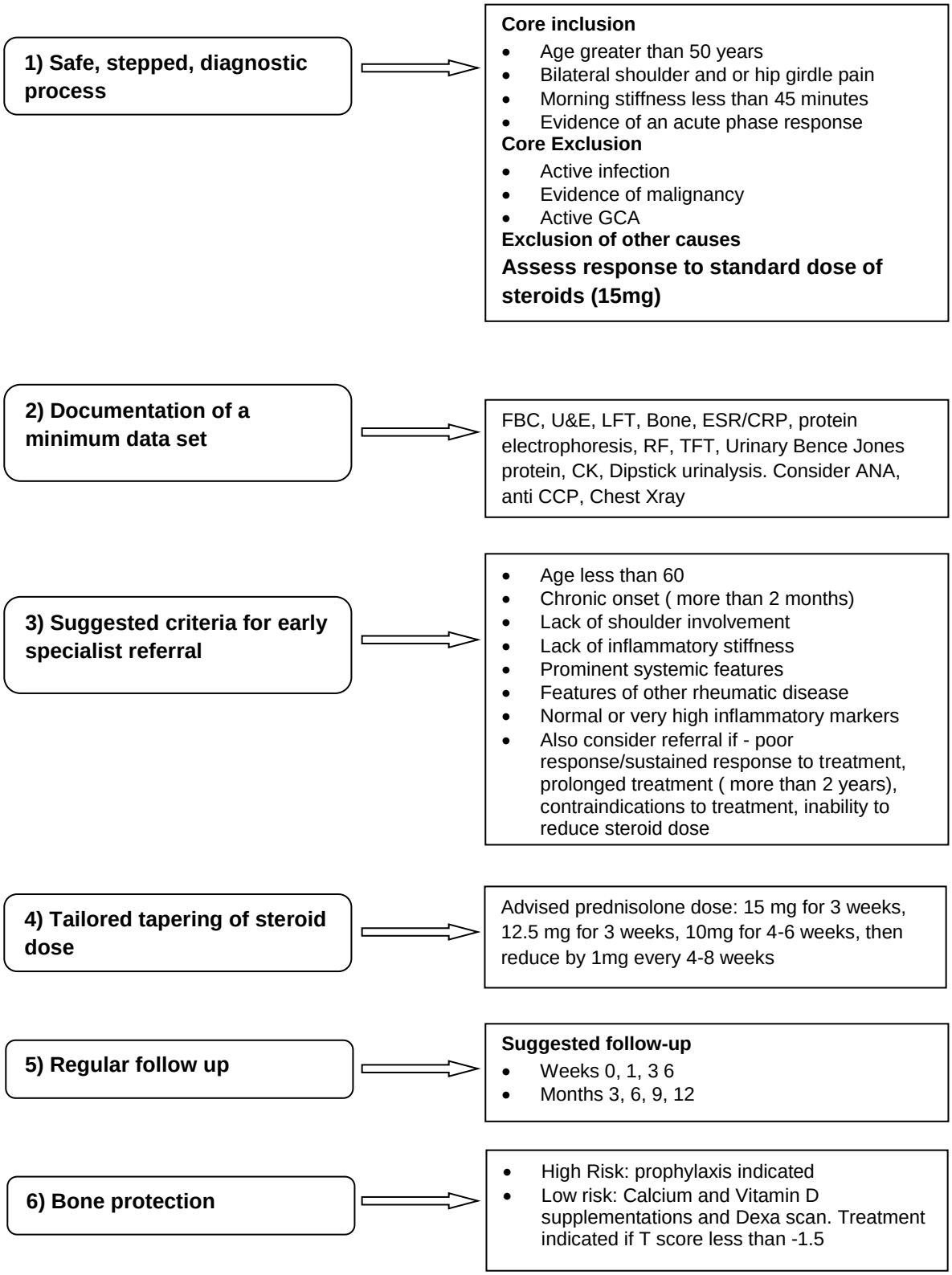


Figure developed from BSR and BHPR guidelines [Dasgupta et al 2010]

1.5.2 Brief review and summary of the literature investigating PMR in the primary care setting

The following section describes in brief a scoping investigation of the literature relating to PMR in primary care.

1.5.3 Methods used in identifying the literature investigating PMR in the primary care setting

To understand the extent of research conducted on PMR in primary care and to inform the original research planned for this thesis, an exploratory scoping literature search of Medline and Embase was conducted for primary care focused studies (September 2011). The search term “polymyalgia rheumatica” and the thesaurus explode function (which allows all related terms to be included in the search) was used for both Medline and Embase to identify PMR studies. This was combined with a search undertaken again using the thesaurus explode function searching for “primary care”, “general practice” and “family medicine”. The abstracts of identified studies were then reviewed to identify original research studies with a focus on general practice. 14 full text studies were identified, three of which have already been discussed, as they were epidemiology studies. An additional study [Helliwell et al 2013] was identified subsequently to the initial search and is included in these findings.

1.5.4 Review findings of scoping literature search

The highlights of the identified studies are summarised under the two main themes of diagnosis and management. Articles by Kyle (1985), Salaffi (2005) and Smeeth (2006) were identified but have been presented in the sections relating to epidemiology and Table 1.1 and will not be discussed again.

1.5.4.1 Diagnosis

Studies relating to the diagnosis of PMR in general practice are summarised in Table 1.2.

Barraclough (2008) undertook a study using routinely collected GP consultation data from three general practices in Gloucester, UK. This study aimed to investigate the diagnosis and management of PMR in general practice. 183 patients with PMR were identified. The most common feature used in diagnosis was shown to be proximal muscle pain, which was documented in 82% of patients identified with PMR. Raised inflammatory markers and a significant response to glucocorticoid were other important features used for diagnosis. The study also highlighted that GPs were not using established diagnostic criteria. [Barraclough et al 2008]

Table 1.2 Summary of primary-care based studies relating to the diagnosis of PMR.

Reference	Title	Study Design	Aim	Study Findings
Bahlas 2000	Utilisation and costs of investigations, and accuracy of diagnosis of PMR by family physicians	Retrospective chart review of 123 patients referred to a tertiary rheumatology clinic	To ascertain the costs of PMR investigations and accuracy of diagnosis of family physicians	An accurate diagnosis of PMR was made in 24% of cases There was a high cost associated with investigations for PMR
Barraclough 2008	Polymyalgia rheumatica in primary care: a cohort study of the diagnostic criteria and outcome	Retrospective notes review, three general practices in Gloucester UK between 1994-2003	To identify the features used to diagnose PMR, benchmark these against diagnostic criteria and identify features of diagnostic importance	11% of patients had a normal ESR[a] Most common features documented were: Proximal muscle pain (82%) Raised inflammatory markers (87%) A clinical response to glucocorticoids (91%) Being female and raised inflammatory markers were associated with longer treatment duration. 17% were referred for specialist review
Coomes 1976	A prospective study of 102 patients with the polymyalgia rheumatica syndrome	Prospective observational study	To study prospectively a cohort of patients referred by GPs to a secondary care rheumatology clinic who were diagnosed with either PMR or GCA	Diagnosis mentioned in referral letter correct was correct 4% of the time between 1964-69 and 10% of the time between 1970-74
Cope 1969	Polymyalgia rheumatica in general practice	Case series of 5 PMR patients seen in general practice	To describe 5 cases of PMR encountered in a rural general practice	PMR is a more common disease than expected and in the five cases described, raised ESR[a] and weight loss were constant findings

Reference	Title	Study Design	Aim	Study Findings
Gamez-Nava 1998	Referral and diagnosis of common rheumatic diseases by primary care physicians	Retrospective observational study	To describe the primary care patterns of referral for musculoskeletal disorders.	Probability of a GP detecting PMR (sensitivity) 60%, Probability of a GP excluding PMR (specificity) 98%
Helliwell 2013	Polymyalgia rheumatica: diagnosis, prescribing, and monitoring in general practice	Retrospective observational study	To investigate the diagnostic processes, management, and monitoring of patients with PMR in UK primary care.	Identification and initial management is appropriate. Documentation of a process of exclusion of mimicking disorders and consideration of prophylaxis for potential treatment adverse effects could be improved upon. Referral for specialist review was made in 44.4% of cases
Jones 1981	Polymyalgia rheumatica and giant cell arteritis. a difficult diagnosis	Prospective observational study	To identify the difficulties and challenges associated with diagnosing PMR	Referral of PMR patients to specialist settings are more likely to be those with an atypical presentation and will consequently be more likely to cause diagnostic difficulty. Cohorts of patients from hospital practice alone cannot be considered to present a typical picture of the disease.
Jordan 2010	Consultations for selected diagnoses and regional problems	Retrospective observational study	To illustrate the frequency of consultations in general practice every year for selected musculoskeletal disorders	12 practices contributing consultation data to the Keele GP research partnership. Results presented per 10,000 patients. 12% of all consultations with a diagnosis were for musculoskeletal disorders. 20 were for PMR

Reference	Title	Study Design	Aim	Study Findings
Kremers 2005	Use of physician services in a population-based cohort of patients with polymyalgia rheumatica over the course of their disease	Prospective observational study	Describe the use of generalist and specialist services in a cohort of patients with PMR	39.6% exclusively managed by a general physician 28% had 1 rheumatology review early in the illness There was a trend towards younger patients, patients with a normal/near normal ESR[a] and patients with multi-morbidity being referred for specialist review Majority of care (67%) provided by generalists
Turner 1983	Polymyalgia rheumatica: a general practice experience	Case series review	To describe the natural history, diagnostic challenges and outcomes of 10 patients diagnosed with PMR in general practice.	Only descriptive findings of typical PMR features presented. Author concluded that with an aging population PMR would be more often encountered and that research should include patients recruited from general practice

[a] ESR: erythrocyte sedimentation rate

Helliwell (2013) identified 304 PMR patients from the CiPCA (Consultations in Primary Care Archive) and PiPCA (Prescriptions in Primary Care Archive) databases. These databases consists of frozen consultation, prescribing and investigation data from local participating general practices which are part of the Keele GP Research Partnership (Staffordshire, UK) and undergo on-going training, assessment and feedback to ensure the quality of data and morbidity coding. [Porcheret et al 2004] This study investigated both diagnostic and management issues in general practice. Recording of diagnosis, identification and initial treatment appeared to be in-line with current guidance. However, documentation of a process of exclusion of other diagnoses could be improved upon. [Helliwell et al 2013]

1.5.4.2 Referral for specialist review

PMR in the UK is usually diagnosed and managed in non-specialist settings with referral for specialist review being made for between 17% [Barraclough et al 2008] and 44.4% [Helliwell et al 2013] of potential PMR patients (table 1.3). This finding however, is not confined to the UK. Kremers (2005) showed that 67% of care for PMR patients was provided by generalists in the Olmstead County area in the USA [Kremers et al 2005] whilst Binard (2009) demonstrated that over 40% of GPs who took part in their French study on PMR did not request rheumatology reviews for their patients. [Binard et al 2009]

Table 1.3 Referral rates

Author (Year)	Country (Region)	Proportion referred for specialist review
Barraclough 2008	UK Gloucestershire	17%
Binard 2009	France	41.7%
Helliwell 2013	UK Staffordshire	44.4%
Kremers 2005	USA Minnesota	61.4%

Much has been written about the diagnostic accuracy of a primary care PMR diagnosis. Coomes (1976) suggested that general practitioners diagnosis of PMR was correct in just 4% of cases in their study conducted between 1964 and 1969. This had risen to a diagnostic accuracy of 10% when replicated between 1970 and 1974. This study reviewed 102 patients referred to the rheumatology clinic from general practice over a 13 year period, assessing diagnostic accuracy by reviewing the referral letter to see if PMR had at all been suggested. [Coomes et al 1976]

In a more recent study Gamez-Nava (1998) investigated the referral and diagnosis of common rheumatic diseases by primary-care physicians. They examined referrals made by 305 primary-care physicians (711 consecutive patients) at a university-based outpatients department in Alberta, Canada. They considered the final rheumatologist's diagnosis as the gold standard. Out of the 711 patients referred with different rheumatic disorders, 10 were referred with potential PMR and five patients had a final formal

diagnosis of PMR made, resulting in a calculated sensitivity of 50%. [Gamez-Nava et al 1998]

However, in part this may be explained by differences in reasons for referral. GPs may be less likely to refer patients where they are confident of the diagnosis and as such the PMR patients included in this study are likely to represent diagnostic uncertainty rather than diagnostic error. [Gamez-Nava et al 1998]

Bahlas and colleagues conducted a study investigating the utilisation and costs of investigation and accuracy of diagnosis of PMR by family physicians. This was a retrospective chart review of 123 PMR patients referred to a tertiary rheumatology clinic again in Alberta, Canada. They reported that an accurate diagnosis of PMR was made in 24% of cases and that there was a high cost of investigations associated with its diagnosis. [Bahlas et al 2000] As these were patients finally seen in a tertiary referral centre, it is likely that many were significantly atypical in presentation and so more extensively investigated with accompanying higher costs. As such, it would seem possible that these referrals were appropriate, but that this sample does not reflect the general PMR population.

Kremers (2005) reviewed the use of physician services in a population-based cohort of patients with PMR over the course of their disease. This was based on the previously described Olmstead County cohort, USA. They found that 39.6% of the cohort was exclusively managed by a generalist and there was a trend to refer younger patients, patients with more comorbidities and patients with a normal or near normal ESR. They concluded that referral to a rheumatologist is driven by diagnostic uncertainty. Referral at times of diagnostic uncertainty is reflected in the current UK guidance which advises

referral for specialist review in younger patients, patients without shoulder involvement, normal or very high inflammatory markers, features suggestive of other rheumatic disease, prominent systemic features (for example significant weight loss or neurological signs) and treatment dilemmas (for example poor response to initial treatment or an inability to reduce the dose). [Dasgupta et al 2010]

An alternative estimate of diagnostic accuracy is made by Quick (2012) who presented data from a rapid access specialist PMR clinic based in Bristol, UK. The clinic protocol encouraged referral of all potential cases of PMR from local general practices prior to treatment with glucocorticoids so that the patients' presenting symptoms were not affected. 55% of patients referred to this clinic were confirmed cases of PMR. [Quick and Kirwan 2012] However, GPs may well have excluded PMR (as did the clinic) based on a poor response to treatment. Additionally, because of the low threshold for accepting potential suspected PMR patients, referrals may be done early and without a period of consideration that may have happened prior to the service becoming available. This therefore impacts on the accuracy of the study findings but does give a closer and more accurate estimate of clinical diagnostic accuracy when compared to the secondary care focused studies already described.

1.5.3 Management

UK published guidelines recommend that in uncomplicated cases of PMR management should be undertaken in the community. [Dasgupta et al 2010] It was not however, until

these guidelines were published that a complete management process was brought together in a single guideline.

Currently, the most accepted form of treatment is with low-dose glucocorticoids, typically at an initiating dose of 15mg of prednisolone followed by a slow reduction in dose over a period of 18-24 months. This suggested treatment regimen is summarised in Box 1.1

Box 1.1 Suggested glucocorticoid treatment and dose reduction regimen

Initial dose 15mg prednisolone for 3 weeks

Reducing in prednisolone dose

- **12.5mg for 3 weeks**
- **10mg for 4 to 6 weeks**
- **Reduction of 1mg every 4-8 weeks**

Symptom flares managed by increasing dose of prednisolone to previous dose that controlled symptoms

Adapted from BSR/BHPR guidance [Dasgupta et al 2010]

Treatment with glucocorticoids may be required for two years or more and as such management strategies need to account for any potential adverse treatment effects (Box 1.2). Appropriate prophylaxis for example bone protection (with calcium and vitamin D supplementation and bisphosphonates if indicated) or gastric protection (with proton pump inhibitors) in high risk groups to prevent glucocorticoid adverse effects should be therefore considered and instigated if indicated for patients taking long term glucocorticoid treatment. This is especially important as patients are particularly concerned about glucocorticoid side effects. [Twohig et al 2015, Helliwell et al 2015] Box 1.2 summarises some of the identified adverse effects of glucocorticoids.

Box 1.2 Potential adverse effects of glucocorticoid therapy

Gastrointestinal

- Dyspepsia, Pancreatitis, Peptic ulceration and perforation, Oesophageal ulceration and Candidiasis.

Musculoskeletal

- Muscle weakness, Osteoporosis, Vertebral/long bone fracture, Tendon rupture

Endocrine

- Diabetes, Menstrual irregularities, Hirsutism, Weight gain, Raised cholesterol, Hyperlipidaemia,
- Increased susceptibility to infections.

Neuro-psychiatric

- Psychological dependence, Insomnia, Raised intracranial pressure, Aggravation of schizophrenia and epilepsy

Opthalmic

- Glaucoma, Papilloedema, Cataracts, Ophthalmic viral or fungal disease, Raised intra-ocular pressure

Additional

- Impaired healing, Ecchymosis, Urticaria, Hyperhydrosis, Skin atrophy, Bruising, Myocardial rupture post recent myocardial infarction, Congestive cardiac failure, Leucocytosis, Headache, Vertigo

Source: British National Formulary [BNF.org]

The studies relating to the management of PMR are summarised in Table 1.4. Chantler (2003) found that the most common rheumatological indications for prescribing long-term glucocorticoids in women over 50 years of age were PMR and rheumatoid arthritis. In patients aged over 70 the most common reason for long-term glucocorticoids was PMR. [Chantler et al 2003]

Table 1.4 Studies investigating the management of PMR in primary care

Reference	Title	Study Design	Aim	Study Findings
Binard 2009	Validity of the polymyalgia rheumatica activity score (PMR-AS) in primary care practice	Clinical vignettes study	To assess the reliability of the PMR-AS for assessing relapse of PMR in primary care.	35.8% of GPs routinely referred PMR patients to rheumatology for diagnosis 41.7% reported that they do not routinely arrange a rheumatology review for PMR patients PMR-AS is valid to be used by GPs (previously only valid for use by rheumatologists) in identifying relapse of PMR
Chakravarty 1994	A district audit on the management of PMR and GCA	Cross sectional regional questionnaire survey of rheumatologists and GPs	To evaluate the role of ESR[a] and CRP[b] in diagnosis and monitoring of PMR; and the dose and duration of corticosteroid treatment to help develop regional consensus guidelines.	Initiating steroid dose and steroid tapering varied widely (same for consultants). Wide variation in community and hospital use of diagnostic tests. There was an over reliance on ESR[a] in identifying relapse
Chantler 2003	Oral glucolcorticoid prescribing in women over the age of 50 years and the use of fracture prevention therapy, and bone densitometry	Retrospective observational study	To identify the most common diseases that are being treated with corticosteroid therapy in women over 50 years old	Most common diseases treated with long term glucocorticoids are PMR/GCA and rheumatoid arthritis. PMR and GCA was the most common reason for treatment with glucocorticoids in patients over 70 years of age

[a] ESR: erythrocyte sedimentation rate, [b] CRP: C-reactive protein

Chakravarty (1994) undertook a district audit on the management of PMR. Questionnaires focusing on the management of PMR were sent to both rheumatology consultants and general practitioners .This study achieved a high response rate of 78% from GPs. The study found that there was great variation in the initiating dose of prednisolone and the reduction in prednisolone dose over time by both GPs and specialists. Additionally in both groups it was found that clinicians were over relying on ESR results and not symptoms to identify PMR relapse. [Chakravarty et al 1994] The management of PMR was also investigated by Helliwell (2013) (discussed above in section 1.5.4.1) and although initial treatment was largely in line with current guidance, prophylactic treatment for osteoporosis and or gastric protection was found to not be routine practice. [Helliwell et al 2013]

1.5.4.4 Summary

From the studies identified, it would appear that the accuracy of PMR diagnosis in primary care is variable and that published classification/diagnostic criteria are not frequently used outside secondary care and/or research settings. The reasons for this are not understood and are likely to be multifactorial. Many of these studies were undertaken prior to the publication of clinical guidelines that encompassed all aspects of care. The majority of studies reporting diagnostic accuracy were based on referrals made by GPs to secondary care, yet PMR is predominantly diagnosed and managed in the community with referrals for specialist review being made at times of diagnostic uncertainty or non-response to treatment.

As such, studies of secondary care patient populations will undoubtedly report high rates of diagnostic inaccuracy. [Kremers et al 2005, Gamez Nava et al 1998]

1.6 Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA) or temporal arteritis (TA) is the most common large vessel vasculitis [Dasgupta (GCA) et al 2010] and has a clear association with PMR. [Salvarani et al 2008] Up to 21% of patients with PMR patients will develop evidence of GCA and 40-60% of patients with GCA report PMR symptoms. [Salvarani et al 2008] It is however less common than PMR with an estimated incidence of 2.2 per 10000 patient years. [Smeeth et al 2006] Barraclough (2012) estimated that a full-time general practitioner can expect to see one new case every 1-2 years. [Barraclough et al 2012] However, given the estimates of incidence given by Smeeth, it is likely that GPs will encounter it less often depending on the patient demographic of the practice population.

Classical presenting symptoms of GCA include headache (which may be unilateral and often temporal), scalp pain, jaw and tongue claudication (pain on talking or chewing), constitutional symptoms (for example lethargy and weight loss) and visual symptoms including blurring of vision, amaurosis fugax (temporary, usually unilateral visual loss), diplopia (double vision) and ultimately (if left untreated) blindness. Clinical signs include a clinically abnormal superficial temporal artery (tender or thickened with reduced or absent pulsation), scalp tenderness, upper cranial nerve palsies and pale swollen optic discs on fundoscopy with associated haemorrhages. [Dasgupta et al 2010] These symptoms are usually accompanied by a significant inflammatory response (classically a

raised ESR). Prompt identification, treatment with high dose glucocorticoids and early referral of potential patients with GCA is imperative to prevent potential irreversible blindness.

The diagnosis is frequently clinical, although the gold standard diagnostic test remains temporal artery biopsy (TAB). However, 13% to 19% of patients with typical features of GCA have a negative temporal artery biopsy. [Niederkohr et al 2007, Breuer et al 2008]

Ultrasound scanning is increasingly being developed as a diagnostic test for GCA since it is less invasive and thus more acceptable for patients. It has been shown to have a sensitivity of 69% and specificity of 82% when compared to temporal artery biopsy. [Karassa et al 2005] Positron Emission Tomography (PET) scanning is an alternative, promising imaging technique with a sensitivity of 80% and specificity of 79% when compared to biopsy. [Prieto-Gonzalez et al 2014] However, owing to lack of its general availability and high cost, it is unlikely that PET scanning will become a mainstream imaging modality in the near future for GCA.

Initial treatment is with high dose glucocorticoids typically between 40 and 60 mg of prednisolone per day although intravenous methylprednisolone under ophthalmology observation is advised in patients presenting with visual symptoms [Dasgupta (GCA) et al 2010]. The role of the GP in the diagnosis of GCA involves keeping a high index of suspicion for the disorder and in potential cases initiating early therapy and referring on to appropriate specialist services for diagnostic confirmation. Subsequent to formal diagnosis GPs are often involved in the on-going glucocorticoid reduction and regular

assessment, screening and if indicated, treatment for glucocorticoid related adverse effects.

This thesis is predominantly concerned with the diagnosis and management of PMR in primary care and its associated challenges. However, given its close association with PMR, it would be remiss not to investigate GCA as part of a wider investigation of PMR. The results obtained from the GCA investigation undertaken as part of the PMR research are presented in detail in Chapter 7.

1.7 Conclusions

Despite PMR being described more than 125 years ago, clear gaps continue to exist in the evidence base for this painful and disabling condition. This is especially pertinent in the primary care setting, where the majority of patients are diagnosed and managed. A lack of accepted standard classification criteria and the use of different research methodologies have made comparisons of the identified epidemiological studies challenging, since spectrum bias is a significant limitation of much of the published literature. Primary care research is needed if we are to improve outcomes for all patients with PMR. The following chapter describes the aims and objectives of this thesis.

Chapter 2: Thesis Aims and objectives

2.1 Introduction

This chapter introduces and justifies the overall purpose of the Ph.D., detailing the specific aims and objectives of the thesis.

2.2 Thesis aims

The overall aim of this PhD is to describe the current diagnostic and management practices used by general practitioners caring for patients with polymyalgia rheumatica, to identify the perceived barriers to effective care, and to determine targets for future interventions and educational initiatives that could lead to improvements in patient care. As GCA has a considerable association with PMR a secondary aim of this Ph.D. is to also investigate the identification, diagnosis and management of GCA in general practice.

2.3 Thesis objectives

The aims of the Ph.D. will be achieved through the following specific objectives:

1) To review the published diagnostic and classification criteria available to clinicians working with patients with PMR and explore their utility

Clinicians diagnosing PMR rely on a set of features that can be used to confidently and accurately diagnose the condition. The objective of this review is to perform a systematic literature review of existing research focussing on the diagnosis of PMR

The review will identify the differences between established diagnostic and classification criteria and how they are used in a clinical setting.

2) To determine the current practice for the diagnosis and management of PMR in general practice

This objective will be achieved by conducting a large national cross-sectional questionnaire postal survey of 5000 randomly selected UK general practitioners to investigate the diagnosis and management of PMR in the community.

3) To explore in-depth the barriers and potential solutions to successful primary care diagnosis and management of PMR.

The final objective of this PhD will be realised using semi-structured telephone qualitative interviews with general practitioners focusing on the perceived challenges encountered with diagnosing and managing PMR. Findings from the cross sectional survey be used to inform the topic guide for the qualitative study.

2.4 Thesis novelty and originality

It has been shown that up to 80% of patients with PMR are diagnosed and managed exclusively by their general practitioner [Barraclough 2008], yet most studies have focused on patients recruited from secondary care settings. As highlighted in Chapter 1, the extent of primary care focused research on PMR is very limited. This thesis will contribute new knowledge to the existing literature on PMR by focussing specifically on primary care. By using a combination of quantitative and qualitative methods this thesis will not only determine GPs current clinical practice but will also identify challenges and

barriers in the optimal diagnosis and management of PMR and GCA. Such a mixed methods approach will allow for a more in-depth exploration of the relevant issues and will provide the opportunity to improve patient care and enhance professional education.

Chapter 3: Literature review of diagnostic and classification criteria for PMR and their use in clinical practice

Diagnosis is the process through which a disease is identified and confirmed using distinctive collections of symptoms, signs and investigation results (for example blood tests and imaging). This chapter seeks to investigate the best available evidence and tools available to GPs to accurately diagnose PMR.

3.1. Introduction

Most rheumatic disorders do not have a single distinguishing feature or 'gold standard' diagnostic test that can be used by practitioners to make a definitive diagnosis. PMR is no exception. There is no 'gold standard' diagnostic test and as such clinicians have to rely upon a collection of clinical features, laboratory findings, the exclusion of other pathology, and response to treatment to diagnose the disorder. Classically, PMR presents with bilateral shoulder pain and or hip girdle pain, muscle pain (myalgia) and morning stiffness with raised inflammatory markers and a significant response to low dose corticosteroids. This cluster of clinical features has long been recognised as typical of PMR. [Barber 1957] However, PMR can also present atypically (in around 20% of cases) and given the significant overlap with presenting symptoms with both rheumatological and non-rheumatological disorders, making an accurate diagnosis challenging.

A British Society of Rheumatology (BSR) and British Health Professional in Rheumatology (BHPR) guideline exists to support the diagnosis and management of PMR. [Dasgupta et al 2010] This guideline outlines a stepwise approach to identifying patients with PMR.

However, the diagnostic aspects of the guideline rely on the exclusion of other disorders (for example "*other inflammatory disorders")* which may be challenging, especially for generalist clinicians.

Fries (1994) noted that criteria sets used in research created a "*uniform language,*" which allowed comparisons between studies to be more meaningful and that "*classification and sub-classification criteria define the presence of a particular disease or specific subsets of that disease*" [Fries et al 1994 p454] and aim to separate patients with the disease from those with "*confusable"* disease. However classification criteria are designed for research purposes and whilst published study inclusion criteria have become used as proxy diagnostic criteria for practising clinicians, this may not be appropriate. This is a particularly pertinent issue for PMR where no 'gold standard' test exists. Whilst classification criteria are important for research purposes (as they are helpful in identifying a standard participant or definite case), they may not be so helpful clinically, as more atypical cases may not be covered by classification criteria and those with multimorbidity may be excluded.

Despite the publication of clinical guidelines and classification criteria some of the published studies identified and described in Chapter 1 have highlighted how accurate diagnosis is a particular problem in general practice. [Bahlas et al 2000] A review of patients seen in a fast track PMR clinic in Bristol (UK) suggests that approximately 50% of patients referred to the clinic had a diagnosis of PMR. [Quick et al 2012] However, it is important to note that this is not a typical secondary care clinic, as GPs were encouraged to refer all potential PMR cases and were discouraged from initiating treatment (something that would not be usual clinic practice). Response to glucocorticoids can be

helpful in making an accurate diagnosis. [Dasgupta et al 2010] Indeed making a diagnosis of PMR can be a challenge even for experts. In studies developing classification criteria for PMR international experts identified 68 potential criteria [Dasgupta et al 2008] and 10 of 128 PMR study participants identified by a panel of international rheumatology PMR experts were reclassified as not having PMR by the end of the study. [Dasgupta et al 2012]

Diagnosis therefore is a key challenge for PMR and this review is intended to identify potential diagnostic strategies for general practitioners. Additionally the findings will contribute to the development of the PMR GP questionnaire postal survey and support developing themes for exploration in the qualitative telephone study of general practitioners.

3.2. Aims and objectives

The aim of this systematic literature review is to identify the most useful clinical features in diagnosing PMR.

This will be achieved using the following methods:

1) Perform a systematic literature search of bibliographical databases to identify relevant studies reporting the diagnosis and classification of PMR
2) Systematically review each identified article
3) Collate relevant data to identify appropriate features for clinical diagnosis

3.3. Methods

3.3.1. Medical Databases

The following bibliographical databases were searched to identify relevant articles.

- **MEDLINE**. MEDLINE is a database of articles from a wide range of academic journals that cover medicine, nursing, dentistry, veterinary science and health care as well pure science fields including biology and biochemistry. [http://www.nlm.nih.gov/pubs/factsheets/medline.html]

- **AMED.** AMED is a healthcare database produced by the Health Care Information Service of the British Library. It covers subject areas allied to medical professions including physiotherapy, occupational therapy, podiatry, rehabilitation medicine, palliative care and complementary medicine. It indexes relevant articles from 596 journals, mainly from Europe many of which are often not indexed in other databases. Key journals can also be found on the database. [http://www.ovid.com/webapp/wcs/stores/servlet/ProductDisplay?storeId=13051&catalogId=13151&langId=-1&partNumber=Prod-12]

- **CINAHL.** CINAHL is a research database providing details of articles from journals relevant to nursing, allied health, healthcare and biomedicine. [http://www.ebscohost.com/academic/cinahl-plus-with-full-text]

- **EMBASE.** EMBASE is a bibliographic database of over 7600 biomedical journals from 90 countries that was designed to "*support information managers and*

pharmacovigilance in complying with the regulatory requirements of a licensed drug". Its design allows detailed searches for specific drug adverse events and tracking.[http://www.elsevier.com/online-tools/embase]

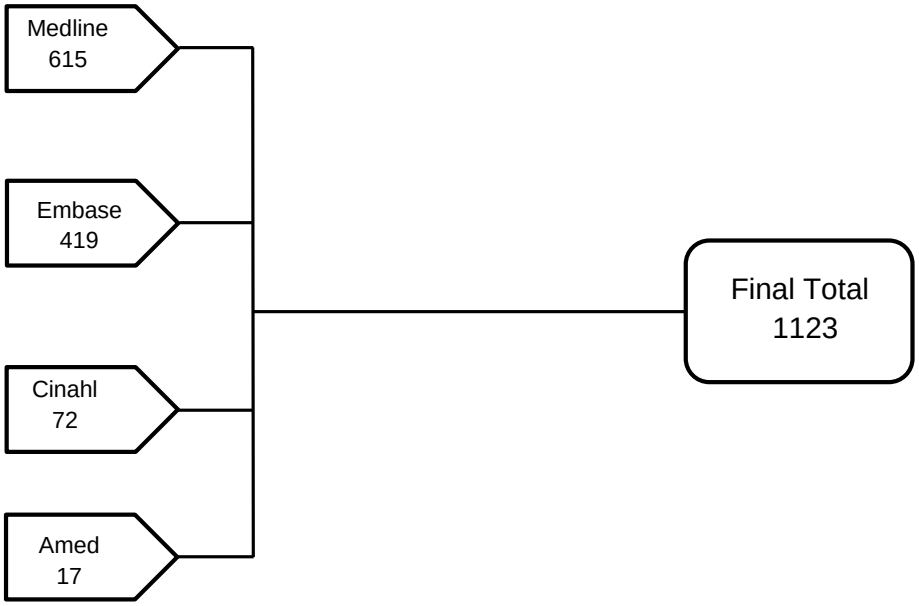
3.3.2. Search Strategy

MEDLINE, CINAHL, EMBASE and AMED databases were individually searched. The search terms used for Medline and EMBASE can be found in [Appendix 1]. These specific search terms were also used for CINAHL and AMED and the searches were repeated using the search engine thesaurus "explode" option. This is a tool that allows all associated terms to also be included in the search.

Particular challenges have arisen with this literature search. The condition of interest is PMR, however there isn't an outcome of interest other than the accurate diagnosis of PMR, making the use of traditional search structures such as PICO (population, intervention, control, outcome) and established search filters unhelpful.

The resulting searches for PMR and diagnosis/classification were combined using the "AND" command and the resulting citations were limited to studies published in English, studies involving humans and studies using participants over the age of 18 years. No limits were imposed on the type of study at the stage of the review. The resulting citations for each database were imported into a Refworks file and then combined, with all identified duplicates being removed. The results of articles identified are summarised in Figure 3.1.

Figure 3.1 Unique citations identified in each database



3.3.3. Selection of relevant articles from identified citations

Identified titles were screened by two reviewers (Toby Helliwell (TH) and Sara Muller (SM)). The following inclusion and exclusion criteria were used to identify studies for abstract review.

Inclusion Criteria

1) The study reported on patients, or a sub-group of patients, with PMR.
2) The study was specifically reporting diagnostic or classification criteria.
3) The study was researching features (clinical, genetic, imaging and laboratory) that may be used to diagnose PMR or distinguish it from other diseases that may present in a similar way.
4) The study was original research or a systematic review using human participants.
5) The study was published in English.

Exclusion Criteria

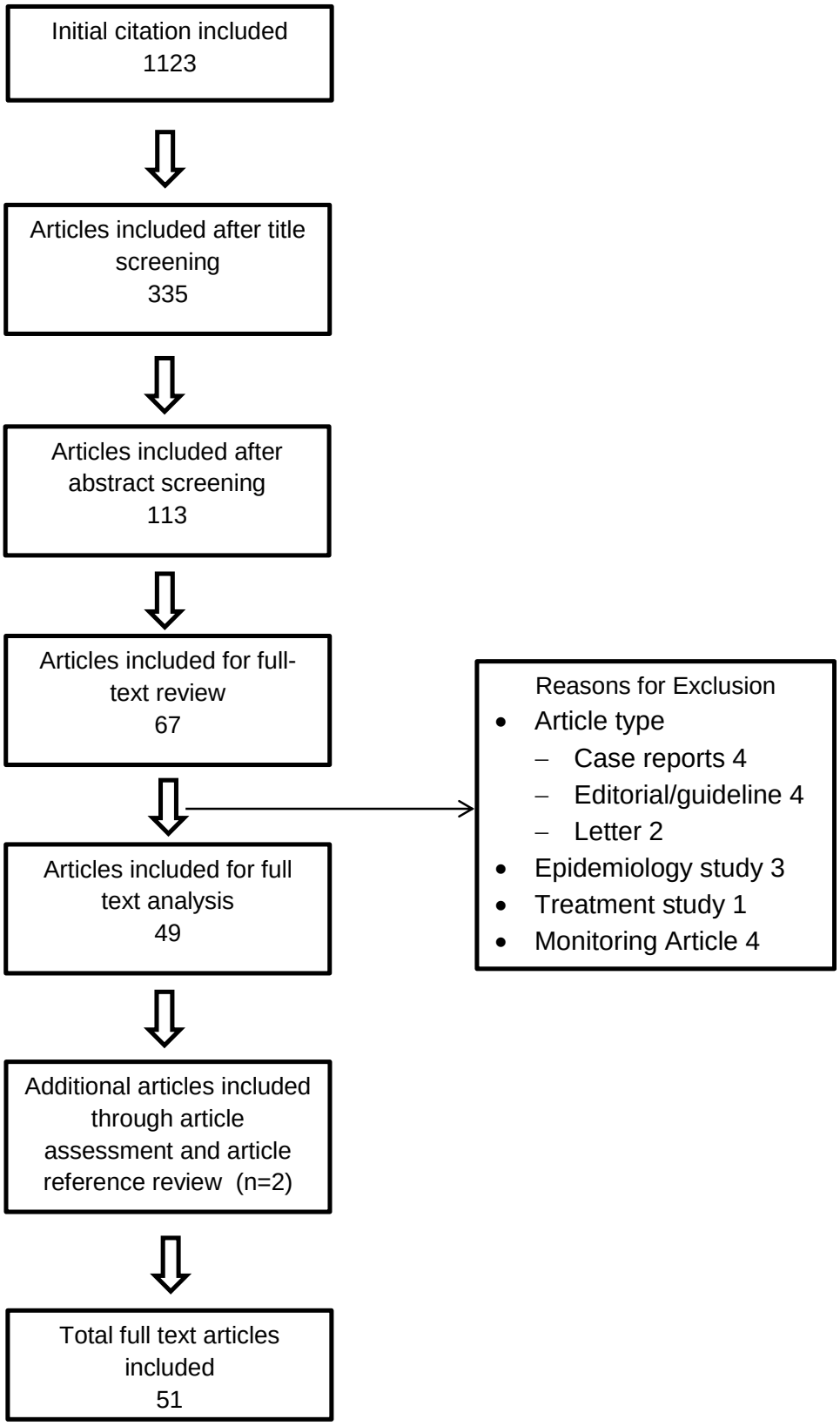
1) Articles reporting on disorders other than PMR
2) Articles that did not research diagnosis or features of PMR at the onset of the disease
3) Articles that were editorials, case reports or case series.
4) Articles not in English

Any title identified as potentially relevant by one or more reviewer was carried forward to the abstract screening stage. The abstracts of titles that met the inclusion/exclusion criteria were obtained for abstract review. Abstracts were then screened (by both TH and SM) to identify studies for full text review. Any study abstract included by one reviewer was reviewed in full text. Finally, of the full text articles identified, the reference lists were further reviewed to identify any additional articles that had not been identified using the formal process described above. This process is summarised in Figure 3.2.

3.3.4. Data extraction and synthesis

A standard data extraction form was created to extract relevant information from the articles including data relating to the objectives, methods, results and conclusions of the article. Information on geographical location, number of patients studied, criteria used and a quality assessment score (discussed below) was also included on the form. The data extraction form can be found in Appendix 2.

Figure 3.2 Identification of citations for review



3.3.5. Quality assessment

The majority of identified studies in this review were observational studies and so a quality assessment tool specifically designed for observational research of musculoskeletal disorders was used. This quality assessment tool derived common themes that were included in identified checklists for observational studies and those used in previous musculoskeletal systematic reviews. [Mallen et al 2007] This instrument has been widely used in musculoskeletal systematic reviews. The quality of each study was assessed using this 15 item checklist which can be found in full on the data extraction form in Appendix 2. Examples of criteria include rates of participation (including descriptions of losses and completers), appropriateness of study question and associated study population. Quality scores (from a maximum score of 15) are presented in the first column in each table.

3.4. Results

3.4.1 Methodological Quality assessment

All studies included in this review were assessed for methodological quality. Studies were not excluded on the basis of the quality score, however this was taken into account when synthesising the evidence. The majority of quality assessment scores were high, with Li (2010) recording the lowest scoring study (10/15) and Dasgupta (2012) the highest scoring (14/15). No studies undertook a formal sample size calculation, however this may not have been appropriate for some of the studies identified. Studies recruiting participants solely from secondary care were deemed to be non-representative as

patients referred to secondary care have been shown to have different characteristics to primary care patients (e.g. more severe disease, non-response to treatment, atypical presenting features) and as such these studies are unlikely to be representative. [Kremers et al 2005]

3.4.2. Study review

51 studies were included for full text review. Of these studies, only five studies recruited participants from a primary care setting. Broadly the studies cover five domains that might be of interest in helping to diagnose PMR in primary care. These are discussed in detail in the following sections.

3.4.3 Classification research studies

These studies relate to investigations that specifically validate existing or new classification criteria or studies that have developed classification criteria which subsequently have been used in other studies investigating PMR and are summarised in Table 3.1.

Table 3.1 Summary of studies investigating classification criteria for PMR

Citation	Overview of study
Bird (1979)	UK (Multi-centre) 146 secondary care "unequivocal PMR" patients 253 controls Criteria tested on submitted data
Bird (2005)	International multi-centre study 213 secondary care patients Criteria tested on recruited participants diagnosed with PMR by expert.
Dasgupta (2008)	International 3 stage hybrid consensus approach 27 World experts consulted to identify key features for classification of PMR
Dasgupta (2012)	International multi-centre study 128 PMR patients, 184 controls Primary and secondary care
Nobunaga (1989)	Japan 29 PMR 119 controls Retrospective case review and development of criteria from identified common features
Chuang (1982)	USA Community epidemiology project of PMR No detail of how criteria were developed for use in this study
Jones/Hazelman (1981)	UK Criteria developed for inclusion of patients to their study on PMR and GCA No detail of how criteria were developed for use in this study

3.4.3.1 Key findings

Seven studies were identified from the literature that specifically presented research related to classification criteria. These are summarised in Table 3.2. Bird (1979) was the first to propose a standard set of classification criteria. This study is summarised in Table 3.2 and whilst achieving three of the criteria performs well at identifying definite PMR cases, the authors stress that their use should be confined to research settings rather than clinical settings. This is because the criteria were not developed and validated for diagnostic purposes but to identify an acceptable research standard with a high probability of having PMR.

Table 3.2 Studies investigating classification criteria for PMR

First Author (quality assessment score)	Objective	Findings or criteria identified
Bird 1979 (12/15)	To identify a reproducible means of identifying PMR for research	Bilateral Shoulder Pain and or stiffness Onset of illness less than 2 weeks duration Initial ESR[a] more than 40 mm/hour Morning stiffness more than 1hour Age greater than 65 Depression and or loss of weight Upper arm tenderness bilaterally **The presence of 3 criteria achieves a sensitivity of 92% for PMR**
Dasgupta 2008 (NA: consensus study of world experts, patients not recruited)	To identify classification criteria for PMR	Candidate criteria identified for a prospective PMR study investigation. These included for further study: Age greater than or equal to 50 years Duration of more than 2 weeks Bilateral shoulder and/or pelvic girdle aching Duration of morning stiffness of more than 45 minutes Elevated ESR[a] or CRP[b] Rapid steroid response (greater than 75% global response within 1 week to prednisolone/prednisone 15 to 20 mg daily)
Dasgupta 2012 (14/15)	To develop a EULAR/ACR classification criteria for PMR	Morning stiffness (2point) Hip pain/limited range of movement (1 point) Absence of RF[c]/Anti CCP[d] (2 points) No other Joint pain (1 point) **Score greater than or equal to 4:-Sensitivity 68%,Specificity 78% (PMR versus other similar disorders)** **Inclusion of positive relevant ultrasound findings Sensitivity 66% Specificity 81%**

First Author (quality assessment score)	Objective	Findings or criteria identified
Nobunaga 1989 12/15	To propose specific criteria sets for PMR in Japanese patients.	Bilateral myalgia for 2 weeks and symptoms of at least 2 of neck, shoulders, shoulder girdle, upper arms, hips or pelvic girdle and thighs Normal serum myogenic enzymes ESR[1] greater than 40 No swelling in the hand joints **Presence of all 4 features: 93.1% sensitivity 98.3% specificity**
Jones/Hazelman 1982 (N/A: study did not relate to the criteria used)	Classification criteria developed for recruitment of patients to their study investigating the link between PMR and GCA	Shoulder or hip girdle pain Morning stiffness Disease duration 2 months or more ESR[a] greater than 30 or CRP[b] greater than 6, Absence of rheumatoid arthritis Absence of muscle disease Age greater than 50 year
Chuang 1982 (N/A: study did not relate to the criteria used)	Classification criteria developed for recruitment of patients to their epidemiology study of PMR	Age greater than 50 years Bilateral aching /tenderness for 1 month or more of: neck or torso, shoulders or upper arms, hips or thighs ESR greater than 40 Exclusion of other causes
Bird 2005 (12/15)	To compare performance of different criteria sets for PMR	Bird criteria (3 or more) Sensitivity 99.5%, Jones Hazelman (All criteria) Sensitivity 84.9% Hunder/Chuang (All criteria) Sensitivity 93.3% Nobunga (4 or more) Sensitivity 67.8%

[a]ESR: Erythrocyte sedimentation rate
[b]CRP: C-reactive protein
[c]RF: Rheumatoid factor
[d]Anti CCP: Anti-cyclic citrullinated peptide antibody

Additionally the author highlights that the study does not identify any new, unknown or novel features of PMR that may be important in diagnosing PMR but rather is a validation of a set of existing recognised features as a standard for research purposes. [Bird et al 1979]

Nobunaga (1989) proposed that Japanese patients with PMR may need different criteria since previously described classification criteria were largely based on patients of white Caucasian ethnicity. They identified patients with a diagnosis of PMR and retrospectively reviewed their medical records identifying the relevant clinical features, investigations, imaging and responses to treatment. This allowed them to develop specific classification criteria for Japanese patients that differ from other criteria in that they include the presence of normal myogenic enzymes (for example creatinine kinase) and the absence of swelling in the hand joint. These are summarised in Table 3.2. [Nobunag et al a 1989]

A consensus process undertaken in Dasgupta (2008) informed the design and domains of interest for a future prospective study by assessing the reliability of identified criteria. This study identified 68 different features of PMR deemed important by international experts when diagnosing PMR. [Dasgupta et al 2008] This large number of items is likely in part to reflect the wide variation in PMR presentation and the lack of agreement, even amongst experts, as to the defining features of PMR. The subsequent international prospective study tested the identified criteria and developed a scoring system that had a sensitivity of 68% and specificity of 78% for identifying PMR. [Dasgupta et al 2012] The study challenged the response to glucocorticoid treatment as a reliable feature for classifying PMR, as it did not significantly add to the overall sensitivity of the criteria and did not alter the specificity.

The authors conclude that:

> *"patients aged 50 years and older presenting with bilateral shoulder pain and elevated CRP and or ESR can be classified as having PMR in the presence of morning stiffness for more than 45 minutes, and new hip pain in the absence of peripheral synovitis or positive rheumatoid arthritis serology"*
>
> **Dasgupta et al 2012.P491**

They also stress that whilst their classification criteria are useful for research purposes, they should not yet be used for clinical purposes and should be viewed as provisional even though the criteria set presented achieved a C statistic of 81% (a C statistic of greater than 80% is, conventionally acceptable for use in clinical decision making).

Two further studies are presented in this section. These were not identified from the formal literature search but found from the wider literature. Chuang (1982) and Jones (1981) were not identified in the initial literature search but were identified on review of the studies discussed above. It is likely that these studies were not identified despite the wide inclusion criteria and search terms as the criteria were developed to standardise inclusion to their respective studies (epidemiology of PMR (Chuang) and investigating the link between PMR and GCA (Jones)).

Chuang/Hunder criteria [Chuang et al 1982] were developed to identify patients to recruit to their PMR epidemiology research in Rochester (Minnesota, USA). Their criteria were:

1) Age greater than 50 years
2) Bilateral moderate/severe aching and stiffness for more than 1 month involving 2 or more of the following areas: neck or torso, shoulder or upper arms, hip or proximal thigh.
3) ESR >40 mm/hr (although if this criterion was not met but other features to suggest the diagnosis were present (e.g. a significant and prompt response to corticosteroids) then PMR should be considered).
4) No other cause for symptoms (e.g. the presence of rheumatoid arthritis or multiple myeloma).

These criteria were also used in their follow up studies and have been employed by many other studies subsequently (e.g. Ceccato (2006), Proven (1999)). However, no discussion or validation description is given explaining how the criteria were derived.

Jones and Hazelman undertook a study to retrospectively investigate the association between PMR and GCA.

The criteria that they used were:

1) Shoulder and pelvic girdle pain (primarily muscular)
2) Morning Stiffness (duration not defined)
3) Duration of at least 2 months if not treated
4) ESR of > 30mm/hour or CRP > 6 μg/ml
5) Absence of inflammatory arthritis or malignant disease
6) Absence of objective signs of muscle disease
7) Prompt and dramatic response to systemic corticosteroids

[Jones and Hazelman 1981]

Again, no details were given as to how these classification criteria were developed. These criteria have been used in many PMR studies despite lacking important details on their derivation and a lack of definition for the various criteria for example what constitutes a dramatic response to glucocorticoids or how long do you need morning stiffness for?

Bird (2005) revisited the commonly used classification criteria to assess the sensitivity of each set in identifying PMR. 213 patients with PMR were identified by rheumatology experts and each of the criteria assessed for sensitivity in identifying PMR. The Nobunaga (1989) criteria were the worst performing set but this is unsurprising given that they were developed specifically for a Japanese population. The Bird (1979) criteria had the highest sensitivity however, all participants were recruited from secondary care and they point out that there may be a bias towards their criteria in classifying PMR clinically as it is one of the most commonly used classification criteria and the one that was developed first. [Bird et al 2005]

3.4.4 Clinical Features

Studies relating to the investigation of the presenting signs and symptoms that suggest PMR are presented in Table 3.3.

Table 3.3 Summary of studies investigating the presenting features of PMR

Citation (Year)	Overview of study
Andrews (1965)	UK. Secondary care Mixed prospective (10 PMR patients) and retrospective (34 PMR patients) study Three years of follow-up
Barraclough (2008)	UK. Primary Care 183 PMR patients. Retrospective cohort study Two years post diagnosis follow-up
Caporali (2001)	Italy. Secondary care 116 PMR patients. Prospective cohort 18 months follow-up
Fauchald (1972)	Norway. Secondary care 94 PMR patients. Prospective cohort 8-96 month follow-up
Gonzalez-Gay (1997)	Spain. Secondary care 201 PMR patients. Retrospective case review 18 months of follow-up or greater
Gonzalez-Gay (1998)	Spain. Secondary care 225 patients. Retrospective case review
Gran (2000)	Norway. Community and secondary care 231 PMR patients. Prospective cohort Follow-up until disease remission
Kimura (2012)	Japan. Secondary care 151 patients (RS3PE[a] and PMR). Retrospective cohort case review
Li (2010)	Hong Kong. Secondary care 44 patients. Retrospective case review
Little (2004)	UK. Secondary care 183 patients with small vessel vasculitis. Retrospective case review Follow up, up to 12 years
Narvaez (2001)	Spain. Secondary care 163 PMR patients. Retrospective case review Follow-up until death or cessation of treatment
Olivio (1996)	Italy. Secondary care. 75 PMR patients and 22 EORA[b] with PMR like onset. Retrospective case review

Citation (Year)	Overview of study
Pease (2005)	UK. Secondary care 349 PMR patients. Prospective cohort Minimum follow up of two years
Pease (2009)	UK. Secondary care. 147 patients with EORA[b]/PMR. Prospective cohort Five year follow up
Pege-Regosa (2005)	Spain. Secondary care. 118 patients with PMR, 112 patients with CPDD[c]. Prospective cohort Follow up for at least 12 months
Salvarani (1998)	Italy. Secondary care. 177 PMR patients. Prospective cohort. Follow up 23 months

[a]RS3PE: Remitting seronegative symmetrical synovitis with pitting edema
[b]EORA: Elderly onset rheumatoid arthritis
[c]CPDD: Calcium pyrophosphate deposition disease

3.4.4.1 Key findings

The key findings of the studies relating to clinical features are summarised in Table 3.4. All but one of the identified studies investigating clinical features were undertaken using data obtained (whether prospectively or retrospectively) from patients recruited from secondary care settings. These studies broadly describe either the clinical manifestations of PMR or focus on distinguishing PMR from other selected disorders that can mimic PMR (including elderly onset rheumatoid arthritis (EORA), RS3PE (remitting seronegative symmetrical synovitis with pitting oedema and small vessel vasculitis (SVV)).

Table 3.4 Studies investigating the presenting features of PMR

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Classification criteria used
Andrews 1965 (11/15)	To review the PMR "Syndrome" and its relationship with GCA	Features of PMR: Abrupt onset Early morning stiffness Night Sweats Depression Raised ESR[a] Females affected more than men PMR and GCA appear to be separate entities	Own criteria
Barraclough 2008 (12/15)	Identify features used to diagnose PMR by GPs and compare to recognised diagnostic criteria.	Features used by GPs to diagnose PMR Muscle Pain 82% Raised Inflammatory markers 87% Response to glucocorticoids 91% Normalization of inflammatory markers 81%	Bird Hunder Healy Hazelman
Caporali 2001 (12/15)	To investigate if PMR patients and patients with RA with a PMR-onset show distinctive clinical/laboratory features	No clinical or laboratory feature found , which identifies patients who present like PMR who will develop RA	For PMR: Jones/ Hazelman For RA[b]: American College of Rheumatology RA[b] criteria
Fauchald 1972 (11/15)	To compare clinical, lab findings and clinical course in patients with GCA and PMR	All patients felt symptomatically 'weak' (not further defined) Weight loss in PMR (49%), Fever in PMR (85%)	No stated criteria

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Classification criteria used
Gonzalez-Gay 1997 (12/15)	To investigate the role of ESR[a] in the diagnosis and prognosis of patients with PMR	20.4% of patients had a low ESR[a] (less than 40mm/hr) Low ESR[a] found in men, younger patients and had a less severe disease Also, less abnormalities in other investigations for example haemoglobin levels	Own Criteria`
Gonzalez-Gay 1998 (13/15)	To describe features to identify PMR, PMR with biopsy proven GCA and GCA with no features of PMR	Patients with GCA and PMR were significantly older than the other 2 groups Patients with GCA and PMR had more constitutional symptoms, anaemia was more frequent and had higher platelets and higher ESR[a] compared to other groups	No quoted classification criteria
Gran 2000 (13/15)	To evaluate incidence and peripheral arthritis in PMR & incidence of RA[b] among such cases	4.8% developed RA[b], 38.5% of PMR patients developed peripheral arthritis at some point No clinical or laboratory features identified to distinguish PMR patients subsequently developing RA[b]	For PMR: Bird For RA[b]: American College of Rheumatology RA[b] criteria
Kimura 2012 (12/15)	To compare the clinical features of RS3PE[c] with PMR patients	All RS3PE[c] patients identified (n=28) fulfilled the diagnostic PMR criteria RS3PE[c] patients were more likely to be male and have pitting oedema of their hands compared to PMR patients	Hunder
Li 2010 (10/15)	To examine clinical characteristic of PMR in a Chinese cohort and compare this to Caucasian series	Chinese patients have a significantly longer duration of symptoms prior to diagnosis	Bird (Caucasians) ICD10 for Chinese

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Classification criteria used
Little 2004 (11/15)	To review patients with SVV[d] misdiagnosed as having PMR	13% of SVV[d] patients had a prior diagnosis of PMR Patients with PMR symptoms and microscopic haematuria/proteinuria should be referred to nephrology	No quoted classification criteria
Narvaez 2001 (12/15)	To evaluate the incidence and characteristics of musculoskeletal manifestations in PMR and GCA	20% of PMR patients had clinically detectable peripheral synovitis Distal musculoskeletal manifestations were not uncommon in PMR patients but are in GCA	For PMR: Chuang For GCA: American College of Rheumatology GCA criteria
Olivio D 1996 (12/15)	Examine at onset the clinical and laboratory features of PMR and EORA[e] with PMR like presentation	More Fever and asthenia in PMR, No differences in laboratory tests but RF+ve good predictor of EORA[e], Arthritis of peripheral joints more common in EORA[e]	For PMR: Bird For RA[b]: American College of Rheumatology RA[b] criteria for EORA[e]
Pease 2005 (12/15)	To ascertain demographic and clinical differences between EORA[e], PMR, GCA in patients with polymyalgic symptoms	9 PMR patients developed RA (diagnostic delay of 13 months) No single lab or clinical feature to distinguish EORA[e] from PMR RhF +ve status is a strong indicator of EORA[e] but is not diagnostic	For PMR: Bird For RA[b]: American College of Rheumatology RA[b] criteria for EORA[e] For GCA: American College of Rheumatology GCA criteria
Pease 2009 (13/15)	To attempt to develop a diagnostic algorithm that could help distinguish PMR from EORA[e]	Combination of Wrist and proximal interphalangeal and or metacarpophalangeal joint disease at onset was highly suggestive of EORA[e]	For PMR: Bird For RA[b]: American College of Rheumatology RA[b] criteria for EORA[e]
Pege-Regosa 2005 (13/15)	To describe [f]CPDD mimicking PMR	Proximal symptoms of [f]CPDD can mimic PMR Tibio-femoral OA, tendinous calcifications, ankle arthritis are suggestive of [f]CPDD	For PMR: Chuang For [f]CPDD: McCarty criteria [McCarty 1975]

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Classification criteria used
Salvarani 1998 (12/15)	Determine the frequency and characteristics of distal musculoskeletal manifestations in PMR	45% of PMR patients have distal musculoskeletal manifestations 25% have peripheral arthritis, 14% have carpal tunnel syndrome 12% distal extremity swelling and peripheral arthritis These manifestations were more common in women	For PMR: Healy For RA[b]: American College of Rheumatology RA[b] criteria

[a]ESR: Erythrocyte sedimentation rate
[b]RA: Rheumatoid arthritis
[c]RS3PE: Remitting seronegative symmetrical synovitis with pitting edema
[d]SVV: Small vessel vasculitis
[e]EORA: Elderly onset rheumatoid arthritis
[f]CPDD: Calcium pyrophosphate deposition disease

There are no specific laboratory tests or clinical manifestations that can be used to accurately distinguish EORA with a PMR like onset from PMR. There are features that are "suggestive of EORA" (e.g. being positive for rheumatoid factor [Pease et al 2005] and having distal joint involvement, particularly wrist and proximal inter-phalangeal or metacarpo-phalangeal joint involvement [Pease 2009]), but these are neither sensitive (the proportion of "true" positives people who test positive for the disease among those who have the disease) or specific ("true" negatives ie the proportion of patients known not to have the disease, who will test negative for it) enough for accurate early diagnosis. Similar conclusions have been made for remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) although this disorder (unlike PMR) is more likely to occur in men presenting with PMR like symptoms with associated pitting oedema of their hands. [Kimura et al 2012]

Pease and colleagues identified that just over 6% of the patients who were diagnosed by a rheumatologist using established classification criteria as having PMR were subsequently re-classified as having EORA (mean delay in diagnosis of 13 months (range 1-30 months)). [Pease et al 2005] This has several important implications for primary care. First, careful and regular follow up has to be undertaken, with clinicians being aware of the association of other disorders presenting in a similar manner to PMR and referring on for specialist review if the clinical picture changes (e.g. developing oedema or peripheral arthritis). For GPs this is a challenging area especially as some disorders, (such as remitting seronegative symmetrical synovitis with pitting edema (RS3PE) or calcium pyrophosphate deposition disease (CPDD)) are very rare and the clinician may not have the awareness of these illnesses. The key issue however, is to recognise that the patient is

not following the expected clinical trajectory and to refer early for expert review in such circumstances. Second, research studies need to have adequate frequency and duration of follow up of patients with the same careful assessment and flexibility to change a diagnosis should the need arise.

3.4.5 Laboratory investigations and unique biomarkers

Table 3.5 illustrates the research studies identified from the literature search investigating laboratory tests (including potential novel biomarkers) that could be used to help more definitively diagnose PMR.

Table 3.5 Summary of studies researching laboratory investigations and unique biomarkers in PMR diagnosis

Citation (year)	Overview of study
Arnold (1993)	Australia. Secondary care Prospective cohort. Serum from 30 PMR and 20 control patients to investigate CD8 +ve T lymphocytes
Boiardi (1996)	Italy. Secondary care Prospective cohort. 18 PMR and controls (healthy ≥60, EORA[a] and RA[b] ≤ 50) To assess CD8. Follow up 2 years
Cats (1993)	Netherlands. Secondary care Prospective cohort. 11 GCA, 9 PMR and 25 healthy blood donors To study ANCA[c] in PMR and GCA.
Ceccato (2006)	Argentina. Secondary care. Prospective cohort. 16 EORA[a], 13 PMR patients. To study Anti CCP[d] in PMR. Mean follow up 20.1 months
Chakravarty (1995)	UK. Primary care Prospective cohort. 98 PMR, 100 healthy controls To study aCL[e] antibodies in PMR
Corrigall 1995	UK. Secondary care Prospective cohort. 37 PMR patients and controls (21 rheumatoid arthritis and 27 non inflammatory arthritis eg osteoarthritis) To study CD8 positive T lymphocytes in PMR in comparison to other rheumatic diseases Italy. Secondary care

Citation (year)	Overview of study
Cutolo (2006)	Prospective cohort. Serum of 14 PMR and 15 EORA[a] patients. To investigate serum cytokines in PMR.
Dasgupta (1990)	UK. Secondary care Prospective cohort. Serum from 12 PMR and 3 GCA patients To study IL6[f] in PMR. Follow up 1 year
Elling (1989)	Denmark. Secondary care Prospective cohort. Serum from 55 with PMR and or GCA, 25 controls To study serum CD4 lymphocyte subsets in PMR. Follow up 1 year
Garcia Unzueta (2006)	Spain. Secondary care. Prospective cohort study. Serum obtained from 17 PMR patients To investigate adrenomedullin in PMR
Hachulla (1991)	France. Secondary care Prospective cohort study. Serum obtained from 23 PMR patients. To study serum amyloid A in PMR
Helfgott (1996)	USA. Secondary care. Prospective cohort study. 117 PMR patients. Describe the outcomes of patients with a normal ESR[g]
Kassimos (1995)	UK. Secondary care Prospective cohort study. Serum from 20 PMR and RhF[h] positive controls To study the significance of cytidine deaminase in PMR patients.
Lopez-Hoyos (2004)	Spain. Secondary care Prospective cohort. Serum from 57 EORA[a] patients, 49 PMR and 24 healthy individuals. To Study anti-CCP antibodies[d] in PMR.
Pawlowski, (1990)	Switzerland. Secondary care Prospective cohort. 15 PMR, 17 dermatomyositis and polymyositis patients, 12 healthy subjects Study investigating serum AGP[j] and ACHT[k], to distinguish PMR from dermatomyositis and polymyositis
Proven (1999)	USA. Community based cohort Prospective cohort. 232 PMR patients Study of PMR patients with low ESR[g]
Pulsatelli (1998)	Italy. Secondary care Prospective cohort study. 16 PMR subjects Study of RANTES[m] in PMR. Follow up 6 months
Salvarani (1994)	Italy. Secondary care. Prospective cohort. Serum from 19 PMR and 41 healthy controls Study of CD4 positive lymphocytes. Follow up 6 months
Uddhammar (1995)	Sweden. Secondary care. Prospective cohort. Serum from 23 PMR and 14 Healthy elderly controls Study of CD4 positive lymphocytes. Sweden. Secondary care

Citation (year)	Overview of study
Udehammer (1998)	Prospective cohort. Serum from 15 patients with PMR Investigation of Inflammatory cytokine levels in PMR patients

[a]EORA: Elderly onset rheumatoid arthritis
[b]RA: Rheumatoid arthritis
[c]ANCA: Anti-neutrophil cytoplasmic antibody
[d]Anti CCP: anti-cyclic citrullinated peptide antibody
[e]aCL antibodies: Anti cardiolipin antibody
[f]IL6: Interleukin 6
[g]ESR: Erythrocyte sedimentation rate
[h]RhF: Rheumatoid factor
[j]AGP: Alpha-1-acid glycoprotein
[k]ACHT: Antichymotrypsin
[m]RANTES: Regulated on Activation, Normal T Expressed and Secreted

3.4.5.1 Key findings

20 studies were identified that investigated the role of laboratory investigations or biomarkers and their potential utility in diagnosing PMR. The studies reviewed in this section can be broadly split into 2 groups. First, investigating currently available laboratory tests that can be used to help diagnose and differentiate PMR from other rheumatological disorders (in particular elderly onset rheumatoid arthritis, 4 studies) and second studies that investigate novel biomarkers that could potentially be used to diagnose PMR (n=16). All but one study (Chakravarty 1995) recruited patients exclusively from a secondary care setting using a variety of different classification criteria to identify eligible participants. These studies are summarised in Table 3.6.

Table 3.6 Studies researching laboratory investigations and unique biomarkers in PMR diagnosis

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
Arnold 1993 (12/15)	To assess whether levels of CD8 positive T lymphocytes are useful in diagnosing PMR or GCA	With a CD8 positive T lymphocyte count of less than 22% you have an 88% chance of having PMR. With a CD8 positive count of less than <22% you have a sensitivity of 73% and a specificity of 85%	Jones/ Hazelman
Boiardi 1996 (13/15)	Evaluate the role of CD8 positive T lymphocytes in active PMR and if these can be used to differentiate PMR from EORA[a]	CD8 positive T lymphocytes subsets studied significantly lower in PMR compared to controls Not helpful in distinguishing PMR from EORA[a]	For PMR: Healy For EORA[a]: American College of Rheumatology RA[b] criteria
Cats 1993 (12/15)	To investigate the diagnostic utility of ANCA[b] in patients with GCA and PMR	All patients with GCA positive for ANCA[b] No difference in ANCA[b] between PMR and healthy volunteers	For PMR: Jones/ Hazelman For GCA: American College of Rheumatology GCA criteria
Ceccato 2006 (12/15)	To investigate anti CCP antibodies[c] in differentiating EORA[a] from PMR and anti CCP antibodies[c] in RhF[d] negative EORA[a] patients	In patients with EORA[a], anti CCP antibodies[c] present had a sensitivity of 56%, a specificity of 92% a positive predictive value of 63% and a negative predictive value of 90% A positive anti CCP[c] antibody in patients with PMR symptoms is highly suggestive	For PMR: Chuang For EORA: American College of Rheumatology RA[b] criteria

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
		of EORA[a]	
Chakravarty 1995 (13/15)	Assess anti-cardiolipin antibodies aCL[e] in 98 consecutive patients with newly diagnosed PMR with or without GCA	Increased aCL[e] levels found in 20 patients These had a relative risk of 4.82 in developing GCA at some point during their illness	For PMR: Bird
Corrigall 1995 (13/15)	To assess CD8 positive T lymphocytes in PMR and its potential as a new diagnostic criteria for disease	Reduced percentage of CD8 positive T lymphocytes found in patients with PMR. Specificity of reduced CD8 positive T lymphocytes in PMR 85% (compared to controls with RA[b])	For PMR: Jones/ Hazelman For RA[b]: American College of Rheumatology RA[b] criteria
Cutolo 2006 (11/15)	To investigate serum cytokines and steroidal hormones in PMR and EORA[a]	TNFα[f] raised in all study groups (PMR, EORA[a] and a group of combined PMR/ EORA[a]) IL6[g] was raised in all three groups and significantly raised in the isolated PMR and EORA[a] groups No marker was able to differentiate between the three groups	For PMR: Chuang For EORA[a]: American College of Rheumatology RA[b] criteria
Dasgupta 1990 (12/15)	To investigate IL6[g] in patients with PMR and GCA and to establish additional disease activity markers	IL6[g] raised in PMR/GCA compared to non-inflammatory disorders Known to be raised in RA[b] so unclear how helpful it is in distinguishing from other inflammatory disorders	For PMR: Jones/ Hazelman

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
Elling 1989 (11/15)	To assess CD8 positive T lymphocytes in PMR patients with low or normal inflammatory markers	CD8 positive T lymphocytes lower in PMR with low ESR[h] or CRP[j] compared to controls. T lymphocytes lower in PMR/GCA when inflammatory markers are low or normal	None given
Garcia Unzueta (13/15)	To investigate plasma levels AM[k] in patients with PMR and patients with GCA	AM[k] significantly increased in GCA compared with PMR and controls No differences in AM[k] between PMR and controls	For PMR: Chuang For GCA: American College of Rheumatology GCA criteria
Hachulla 1991 (11/15)	To assess serum amyloid A in the induction of PMR and disease remission with prednisolone	Serum amyloid A: Sensitivity for disease activity (97%) Specificity for inactive disease (86%)	None given
Helfgott 1996 (12/15)	To ascertain the frequency of PMR with a normal ESR[h] and determine defining features	22% of participants had an ESR[h] of less than 30 mm/hr Patients with a high ESR[h] had a significantly lower haemoglobin Low ESR[h] was found to be more common in males Low ESR[h] was associated with a potential delay in diagnosis	For PMR: Jones/Hazelman
Kassimos 1995 (12/15)	To assess cytidine de-aminase in PMR & EORA[a]	Baseline cytidine de-aminase was higher in established pure RA[b] compared to PMR or GCA	For PMR: Jones/Hazeleman For EORA[a]: American College of Rheumatology RA[b] criteria

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
Lopez-Hoyos 2004 (12/15)	To assess the utility of anti CCP antibodies[c] and RhF[d] in the diagnosis of PMR and EORA	No positive anti CCP antibodies[c] found in PMR patients Anti CCP antibodies[c] positive in EORA[a] Anti CCP antibodies[c] in the presence of PMR Symptoms is highly suggestive of EORA[a]	For PMR: Chuang For EORA[a]: American College of Rheumatology RA[b] criteria
Pawlowski 1990 (11/15)	To study the role of α-1-acid glycoprotein and α-1 antichymotrypsin in patients with dermatomyositis/ polymyositis PMR, GCA and healthy controls studied	Presence α-1-acid glycoprotein had a sensitivity of 100% and specificity 88%. Only useful in suspected dermatomyositis/ polymyositis	For PMR: Bird For dermatomyositis/ polymyositis: Bohan 1988
Proven 1999 (13/15)	Determine clinical characteristics of PMR with low ESR in a community based cohort of 232 patients	17 (7.3%) had an ESR[h] <40 No difference in clinical features between the 2 groups	For PMR: Chuang
Pulsatelli 1998 (11/15)	To evaluate the chemokine RANTES[l] in PMR patients at disease diagnosis therapy	Increase levels of RANTES[l] compared to normal Controls, No correlation with clinical and routine lab findings	For PMR: Healey
Salvarani 1994 (13/15)	To measure the levels of soluble CD4 and soluble CD8 in active PMR	Soluble CD8 and soluble interleukin-2R levels were significantly raised in PMR compared to controls (healthy patients). Soluble CD4 decreased in the active phase of the disease	For PMR: Healey

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
Uddhammar 1995 (11/15)	To investigate abnormalities in CD4+ T cell subsets in peripheral blood described for patients with PMR	No difference in number or percentage of T Lymphocytes, HLA DR activated T cells or B Cells CD16 positive CD56 positive lymphocytes suppressed compared to controls until 2 years	For PMR: Bird

[a]EORA: Elderly onset rheumatoid arthritis
[b]RA Rheumatoid arthritis
[c]ANCA: Anti-neutrophil cytoplasmic antibodies
[c]anti CCP antibodies: anti-cyclic citrullinated peptide antibody
[d]RhF: Rheumatoid factor
[e]aCL anti-cardiolipin antibodies
[f]TNFα: Tumour necrosis factor alpha
[g]IL6: Interleukin 6
[h]ESR: Erythrocyte sedimentation rate
[j]CRP: C-reactive protein
[k]AM: adrenomedullin
[l]RANTES: Regulated on Activation, Normal T Expressed and Secreted

3.4.5.2. Investigations and biomarkers currently available in clinical practice

Ceccato (2006) and Lopez Hoyos (2004) demonstrated that the presence of PMR symptoms in patients with positive anti-CCP antibodies should be highly suspicious of elderly onset rheumatoid arthritis (EORA) [Ceccato et al 2006, Lopez-Hoyos et al 2004] with Lopez-Hoyos and colleagues highlighting, that rheumatoid factor was poor at differentiating PMR from EORA. However, these studies used different classification criteria for recruiting their PMR participants making comparison difficult. Furthermore, their utility in a primary care setting might be limited by different availability of these tests for primary care.

Helfgott (1996) and Proven (1999) investigated having a normal ESR in the presence of typical PMR symptoms. These studies differed in their definition of a "normal" ESR (Helfgott defining it as an ESR of less than 30mm/hr and Proven defining it as an ESR of less than 40mm/hr). Helfgott and Kieval noted that patients with a raised ESR tended to have lower haemoglobin levels on laboratory testing whilst both studies failed to demonstrate any difference in the clinical features (duration of morning stiffness, site of stiffness or pain and systemic features for example fever and weight loss) between those with a normal or raised ESR. [Helfgott and Kieval 1996, Proven et al 1999]

3.4.5.3 Novel and experimental investigations and biomarkers

Investigating the utility of new biomarkers is a two stage process. First it is necessary ascertain if the biomarkers level is different in PMR patients compared to healthy controls, and second it is important to assess whether the biomarker is helpful in

differentiating PMR from other rheumatic or mimicking disorders. No novel biomarker has been identified that can accurately diagnose or differentiate PMR from other disorders which commonly present with similar features. The only possible exception to this is α-1-acid glycoprotein (AGP) which is an acute phase protein synthesized by hepatocytes. Pawlowski (1990) demonstrated in a small study comparing 15 PMR patients with 17 patients with dermatomyositis (an autoimmune condition which causes inflammation of the skin and underlying muscle) or polymyositis (an autoimmune condition which causes inflammation of skeletal muscle) and 12 healthy volunteers that the presence of AGP had a sensitivity of 100% for dermatomyositis/polymyositis and a specificity of 88% suggesting that the presence of AGP is likely to exclude a diagnosis of PMR. Dermatomyositis and polymyositis are rare disorders and larger studies are required to replicate these findings and these findings are relevant only to patients with PMR symptoms where there is a possibility of dermatomyositis or polymyositis are being considered. [Pawlowski et al 1990]

The utility of interleukin 6 (IL-6) has been investigated by Dasgupta (1990) and Cutolo (2006). Dasgupta and colleagues in their study of 12 PMR patients demonstrated levels of IL-6 to be raised in patients with PMR which helped differentiate PMR from non-inflammatory disorders (for example osteoarthritis). [Dasgupta et al 1990] IL-6 levels are known to be raised in rheumatoid arthritis [Houssiau et al 1988] but this study failed to compare PMR and other inflammatory rheumatic disorders and clinical utility may be limited.

There has previously been interest in the role of lymphocyte subsets in patients with PMR. Studies have investigated whether the absolute number and percentage of CD8

positive T lymphocytes when compared to controls are useful in diagnosing PMR. However, data is conflicting on the usefulness of CD8 positive T lymphocyte levels in differentiating PMR from EORA. Boiardi (1996) suggest that a reduction in CD8 lymphocytes was not helpful in distinguishing PMR from EORA as only 55% of PMR patients had a reduced number whilst this was also observed in 23% of EORA patients. [Boiardi et al 1996] Corrigall (1995) suggested that participants with normal levels of CD8 positive T lymphocytes and a polymyalgic presentation were more likely to develop seronegative rheumatoid arthritis. [Corrigall et al 1995] Neither of these studies investigated how useful these novel biomarkers would be in conjunction with other laboratory or clinical features. These studies are however limited by the use of different PMR classification criteria (Healy and Jones/Hazelman respectively), and small sample size (18 and 37 respectively). More research in this area needs to be undertaken to clarify these findings further. Furthermore, as neither of these tests is definitively diagnostic or widely available, it is unlikely that they would be useful in everyday clinical practice on the basis of currently published data.

3.4.6 The research of different imaging modalities used in PMR diagnosis

Table 3.7 summarises studies identified that have investigated the role and effectiveness of different imaging modalities to help diagnose PMR.

Table 3.7 Summary of studies investigating different imaging modalities for PMR diagnosis

Citation (year)	Overview of study
Cantini (1999)	Italy. Secondary care Prospective cohort. 23 Pure RS3PE[a], 177 PMR patients assessed by MRI[b]
Cantini (2001(a))	Italy. Secondary care. Prospective cohort. 57 Patients with PMR MRI[b] versus ultrasound assessed
Cantini (2001 (b))	Italy. Secondary care Prospective cohort. 72 patients with PMR 6 case patients with PMR an normal ESR[c] (USS[d] and MRI[b])
Cantini (2005)	Italy. Secondary care. Prospective cohort. 20 patients with PMR, 40 controls assessed by MRI[b]
Falsetti (2002)	Italy. Secondary care Prospective cohort. Ultrasound scans of 50 patients with PMR compared with controls
Falsetti (2011)	Italy. Secondary care. Prospective cohort. 61 patients with PMR, multi-site ultrasound scans
Lange (1998)	Germany. Secondary care. Prospective cohort. Ultrasound scans of 32 patients with PMR
Lange (2000)	Germany. Secondary care Prospective cohort. 51 PMR patients, ultrasound scans of glenohumeral joints

[a]RS3PE: Remitting seronegative symmetrical synovitis with pitting edema
[b]MRI: Magnetic resonance imaging
[c]ESR: Erythrocyte sedimentation rate
[d]USS: Ultrasound scan

3.4.6.1. Key findings

Eight studies were identified investigating the use of imaging in the diagnosis of PMR: four studies considering ultrasound scanning (USS) alone, one study considering magnetic resonance imaging (MRI) alone and three studies investigating MRI and USS. These studies are summarised in Table 3.8.Three studies investigated the effectiveness of imaging at identifying relevant abnormalities that could be used to help diagnose PMR. [Frediani et al 2002, Cantini et al 2005, Cantini et al 2001a] The remaining studies looked at ultrasound scanning as a diagnostic tool to try and help to distinguish between patients with PMR and other rheumatic diseases. (Cantini 1999 (RS3PE), Lange 2000 and 1998 and Falsetti 2011 (EORA)).

For identifying PMR related imaging abnormalities (typically reported as being subdeltoid/subacromial bursitis) ultrasound is as effective as MRI [Cantini et al 2000a & b, Cantini et al 2005] and potentially could be the imaging modality of choice for patients with PMR given its lower cost and relative ease of use. However, the question remains as to whether the presence of these imaging abnormalities, however detected, is sufficient to confidently diagnose PMR and able to differentiate PMR from other rheumatic disorders that present in a similar manner. All of the studies highlighted above attempted to distinguish PMR from elderly onset rheumatoid arthritis (EORA) which can present with a very similar clinical picture to PMR. As an isolated finding it would appear that the presence of subacromial/subdeltoid bursitis is not adequate in reliably distinguishing PMR from EORA [Lange et al 1998, Lange et al 2000] but may be helpful in making a more accurate diagnosis of PMR in conjunction with other clinical laboratory and imaging features. [Falsetti et al 2011].

Table 3.8 Studies investigating different imaging modalities for PMR diagnosis

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
Cantini 1999 12/15	To compare clinical and MRI[a] characteristics of PMR and RS3PE[b]	No significant difference in MRI[a] findings between PMR and RS3PE[b]	For PMR: Healy
Cantini 2001 12/15	Investigation of shoulder structures of PMR patients using USS[c] in patients with normal ESR[d] at diagnosis	Bilateral subacromial/ subdeltoid bursitis represents USS[c] imaging hallmark of PMR both in cases of raised ESR[d] and normal ESR[d]	For PMR: Healy For RA: American College of Rheumatology RA criteria
Cantini 2001(a) 12/15	To compare shoulder USS[c] and MRI[a] in patients with PMR	USS[c] detection of glenohumoral joint synovitis: sensitivity 78.7 specificity 93.3 USS[c] detection of glenohumoral joint bursitis: sensitivity 93.7% specificity 100% USS[c] evidence long head biceps tenosynovitis: sensitivity 100% specificity 100% USS[c] evidence bursitis bilaterally: sensitivity 92.9%, specificity 98.1% USS[c] equally effective with MRI[a] at identifying sub-acromial/subdeltoid synovitis	For PMR: Healy For RA: American College of Rheumatology RA criteria

First Author (quality assessment)	Objective	Summary of main conclusions of the study	Criteria
Cantini 2005 12/15	To investigate hip inflammatory features and evaluate accuracy of examination compared to MRI[a] in patients with PMR	53.4% had pelvic girdle involvement, USS[c] and MRI[a] detected trochanteric bursitis in 100% MRI better for detecting hip synovitis Trochanteric bursitis was the most common hip lesion found on MRI[a] USS[c] was as good as MRI[a] at detecting this	For PMR: Healy For RA: American College of Rheumatology RA criteria
Frediani 2002 12/15	Localization of synovitis in untreated PMR	High prevalence of articular and peri-articular synovitis at onset of PMR Subacromial-subdeltoid synovitis in 70%, Tenosynovitis long head of biceps 68% Glenohumoral joint effusion 66% No significant difference in findings comparing PMR and RA	For PMR: Healy For RA: American College of Rheumatology RA criteria
Falsetti 2011 13/15	Effectiveness of USS[c] at predicting diagnostic outcome in PMR patients	Presence of subacromial subdeltoid bursitis gave an odds ratio of 5.603 for PMR Subacromial bursitis for PMR had a sensitivity of 79% and specificity 59% with a positive predictive value of 64% EORA[e] and the presence of Anti CCP antibodies[f] were found to have more erosions.	For PMR: Bird
Lange 1998 11/15		61.5% demonstrated inflammation of the glenohumoral joints in PMR 63.2% demonstrated inflammation of the glenohumoral joints in the EORA[e] group USS[c] was unable to differentiate between PMR and EORA[e]	For PMR: Healy For EORA[e]: no specific criteria quoted
Lange 2000 12/15	To investigate the usefulness of USS[c] of the glenohumeral joint in PMR and EORA[e]	Glenohumoral joint inflammation found in 40.9% of PMR participants and 65.5% of EORA[e] patients Typical PMR findings: unilateral glenohumoral joint inflammation and discrete biceps tendon sheath effusion	For PMR: Healy For EORA[e]: no specific criteria quoted

[a]MRI
[b]RS3PE: Remitting seronegative symmetrical synovitis with pitting edema
[c]USS: ultrasound scanning
[d]ESR: Erythrocyte sedimentation rate
[e]EORA: Elderly onset rheumatoid arthritis
[f]Anti CCP antibodies: anti-cyclic citrullinated peptide antibody

3.5. Discussion

The overall aim of this systematic literature review was to identify and synthesise the available evidence regarding the diagnosis and classification of PMR, and to consider the findings in order to identify potential challenges in developing a diagnostic algorithm that could be used clinically in primary care. This section brings together the summarised findings for each domain above and will review the strengths and limitations of the systematic review.

3.5.1. Evaluation of the methods used for the review

3.5.1.1. Strengths

Search Strategy

The main strength of this literature review was the systematic approach that was employed to ensure that all studies relevant to classification, or diagnosis of PMR, were included. Search terms were identified from previous PMR based literature reviews and with the help of an experienced health librarian. To ensure maximum coverage, the "explode" feature was used to ensure all relevant and associated search terms were included.

Two reviewers were also used at the title screening stage and all titles identified by either reviewer were kept for abstract screening even where disagreements were present.

Quality

An assessment of the quality of each article was also made using a recognised quality assessment tool. However no studies undertook any sample size calculations and the range of quality scores was between 10 and 14 out of 15. It could be argued that all studies were of high quality. However criticisms include:

- Lack of item weighting as each item is considered equivalent. For example, “an appropriate setting” has an equivalent weight to, “a more than 70% participation”.
- Some items may be viewed as subjective for the assessor for example “an appropriate measure of outcome,” especially in circumstances where there may be a wide variety of outcome measures that could be used.

3.5.1.2 Limitations

Identified citations were limited in the original searches to studies written in English. The general aim of systematic reviews and meta-analyses is to attempt and assimilate all of the evidence available relating to the subject in question. Therefore excluding studies based solely on language goes, in part, against this principle. However, Juni (2002) demonstrated that including all languages has little impact on overall conclusions [Juni et al 2002] although Gregoire (1995) in their review of 36 identified meta-analyses concluded that at least one of the studies would have had different conclusions if all languages had been included. [Gregoire et al 1995] This systematic review may therefore have benefitted from having no language limits, however the risk of a significant citation being missed that would have greatly affected the findings was potentially low, given that

the citations papers identified were submitted from research centres from around the world.

The Cochrane handbook defines publication bias as *"The publication or non-publication of research findings, depending on the nature and direction of the results"* [http://handbook.cochrane.org]. All systematic reviews are at risk of publication bias and therefore a search of un-published articles should have been undertaken. For this systematic review however, most of the published research identified above did not demonstrate significant findings and owing to the limited amount of published research in each area it is unlikely that a significant body of relevant un-published research exists that would alter any conclusions.

Data extraction was undertaken by a single person (TH) and therefore there is the possibility of human error. However, each citation was reviewed twice, first at initial data extraction and then, during citation summary to minimise errors.

3.5.2. Synthesis of results

Owing to the wide variation of the question and the different recruitment strategies used, a meta-analysis was not appropriate and so a narrative approach was taken to data synthesis. Whilst this could be subject to reviewer bias it is the most suitable approach for a review with such a broad focus.

3.5.3 Implications for Practice

This systematic review did not identify any validated diagnostic criteria for PMR nor were there any existing or experimental biomarkers or imagining modality that had diagnostic potential for use in general practice. The GP's approach to diagnosis (in particular for disorders like PMR where no gold standard diagnostic test exists) evolves over time, sometimes through multiple consultations and assessments, which may include responses to trials of treatment in conjunction with relevant investigations, history and examination findings. This contrasts with recruitment into clinical trials where classification criteria are used to identify "standard participants" with a high probability of the disorder whilst excluding atypical patients who still need to be treated in routine clinical practice.

3.5.4. Implications for PMR research

This review has identified several areas that have implications for future PMR research.

1) The lack of a historically recognised and universally accepted classification criteria means that a unified formal definition of PMR for research purposes has been lacking. This means that it has been impossible to formally benchmark laboratory tests, imaging or clinical features against a recognised and agreed "PMR patient". However, the publication of validated and accepted provisional classification criteria should help standardise PMR identification for research, in the future.

2) As no gold standard agreed set of classification criteria exist, at least four different sets of classification criteria have been used. It is also not uncommon for unique criteria to be developed for individual studies. This makes comparison of studies difficult.
3) Most of the studies included in the review have recruited participants from single specialist centres. The question remains however as to how representative patients recruited in secondary care alone are. Future studies should therefore recruit patients from a range of settings and not rely on secondary care samples which are not likely to be generalisable to the wider PMR population.
4) Whilst traditional classification criteria (for example Bird (1979) and Chuang (1982)) may identify definite cases of PMR, it is clear that PMR exists as a spectrum and can present atypically. Future studies therefore may need to include "outliers" to represent this wide spectrum of disease so that results can be generalizable to the wider PMR community.
5) Future prospective studies should ensure adequate long-term follow-up. Disorders mimicking PMR may reveal themselves many months after the PMR diagnosis is originally made, as demonstrated by Pease (2005) where the mean diagnosis of EORA presenting with PMR symptoms was 13 months after symptom onset. [Pease et al 2005]

3.6. Summary

The conclusions of the review are limited in view of the heterogeneity of studies and the small sample sizes of many of the studies identified. No novel or commonly available

group of biomarkers or imaging feature that typically characterises PMR and can be used to definitively diagnose PMR has been identified. Neither is there a single definitive clinical feature or group of features that can be used for reliable diagnosis.

Guidance published by the British Society of Rheumatology and British Health Professionals in Rheumatology in 2010 advocate undertaking an extensive process of exclusion of other causes that may mimic PMR before making a definitive diagnosis. [Dasgupta et al 2010] Whilst for some conditions this requires a simple blood test other differential diagnoses require a certain amount of expertise that generalists may not have. Even with specialist expertise differentiating PMR from other very similarly presenting disorders can be difficult, as demonstrated by the 2012 classification criteria, in which 8% of expert diagnosed PMR was eventually re-classified with an alternative disorder. [Dasgupta et al 2012]

For the generalist, the 2010 clinical guidelines remain the standard process for diagnosis. [Dasgupta et al 2010] Since undertaking this review, up-dated guidance on the management of PMR has been published. [Dejaco et al 2015] Whilst these guidelines focus on the management of PMR, they do reinforce the 2010 guidance advocating a safe and specific approach to diagnosing PMR with a focus on the exclusion of relevant mimicking disorders. This involves undertaking a minimum set of investigations and constant re-assessment at follow up consultations, searching for alternative diagnoses. [Dejaco et al 2015] As no diagnostic feature or group of features have yet been identified to definitively diagnose PMR it may be more appropriate to consider PMR as “suspected” until a sufficient time has lapsed to allow other disorders to present. The existing evidence discussed relies in the majority on assessing the effectiveness of currently

accepted features yet there are a whole range of features that experts use to diagnose PMR [Dasgupta et al 2008] and, as Bird (1979) highlighted, these types of studies do not allow for the identification of new and unique features that might typify PMR. [Bird et al 1979] Given that there is little evidence for specific tests and diagnosis remains challenging, what is needed in the first instance is to investigate the current practices of clinicians. This could be achieved through a large in-depth consultation record review or a large questionnaire study of clinicians involved in identifying and formally diagnosing PMR. For this thesis, and given that there is evidence suggesting that the majority of patients are identified in primary care [Barraclough et al 2008, Helliwell et al 2013] a national PMR questionnaire survey of GPs was undertaken and is described in more detail in Chapters 4 and 5. Specific areas of foci that will be investigated, given the findings of this review, will surround the processes that GPs undertake in making a formal diagnosis for PMR, what alerts them to thinking about potential alternative diagnoses and the kind of investigations used to confirm or exclude PMR.

Chapter 4: PMR National Cross-sectional Survey: methodology

The second objective of this thesis is "*to describe the current diagnostic and management practices used by general practitioners caring for patients with polymyalgia rheumatica, to identify the perceived barriers to effective care, and to determine targets for future interventions and educational initiatives that could lead to improvements in patient care*". This will be achieved by undertaking a nationwide cross-sectional postal questionnaire survey of general practitioners.

4.1. Introduction

This chapter will review the methods used in developing the questionnaire survey and describe the practical aspects of delivering the survey to 5000 participants (GPs), the advantages and disadvantages of this method and potential sources of bias. Finally, the chapter will describe the methods used to analyse the survey data.

4.2. Surveys

Cross-sectional surveys have been widely used for research purposes and range from simple market research to national population based censuses. They can be performed in a variety of ways from individual face-to-face interviews to telephone and self-completion questionnaires. The aim of survey research is to gather standard information from a representative sample. [Aldridge and Levine 2001]

By obtaining data from a representative sample, the conclusions made from the survey findings should reflect the population as a whole.

They are particularly effective if:-

1) new data on a subject are needed;
2) the questions that need to be asked to generate these data are known;
3) the target population is willing to tell you what you need to know;
4) you want to generalise to a whole population.

[Buckingham and Saunders 2009]

4.2.1 Mode of questionnaire administration

Questionnaires can be administered using a number of different methods including face to face interview, telephone interview, self-completion postal questionnaire and increasingly by electronic or on-line methods. The advantages and disadvantages of these different methods are summarised in Table 4.1, however, the choice of method may be limited by the type of research being undertaken. For example face to face interviews may not be practical for a national survey and telephone or electronic methods may be limited if the appropriate contact information is not available.

Table 4.1 Advantages and disadvantages of different survey methods.

Type of Survey	General advantages	General disadvantages
Postal	Relative low cost Quick to perform Can be used to target specific populations Can cover large numbers of respondents Can cover large geographical area No interviewer bias No interviewer effects Effective for sensitive subjects Specific questions can be asked Responses can be controlled Anonymity Ample time to complete questionnaire Complexity Visual aids can be used Convenience	Relatively low response rates Relatively high non-Response bias Volunteer bias Difficult to control context of response Gauging salience of responses Restricts questionnaire length Missing data
Web Based Surveys	Convenience for both participants and researcher Rapid data collection Cost effective Visual aids can be used Ease of follow up Specialist populations can be targeted Complex question processes and decision making tools can be used aided by specific survey software	Limited respondents if contact email addresses not available Self-selection Lack of interviewer involvement
Telephone Surveys	Rapid data collection Possible cost savings Anonymity Assurance that instructions are followed and survey completed appropriately	Potential for: Less control, Less credibility, Less complexity
Face to Face Interviews	Flexibility and opportunity to probe detail and meaning Greater complexity Ability to contact hard to reach populations Assurance that instructions are appropriately followed	High costs Interviewer-induced bias Participant reluctance to cooperate Greater stress Less Anonymous

[Adapted from Rea and Parker 2005]

As part of their study examining recruitment strategies in GP surveys, Bonevski (2011) also questioned participants as to their preferred mode of questionnaire. 81.1% indicated that postal questionnaires were the most preferred format of survey, followed by online (17.1%), face to face (1.7%) and telephone (0.2%). [Bonevski et al 2011]

With increasing use of the internet and the availability of contact electronic details it is likely that on-line and electronic methods (email, on-line questionnaire hosting site e.g. SurveyMonkey and social media portals e.g. Facebook and Twitter) for survey research will be used more frequently in the future.

4.2.2 Postal Questionnaires

Postal questionnaire surveys have the potential to investigate areas of research interest in a population by obtaining data from only a small fraction of that population [Dillman et al 2007]

Postal surveys remain a popular survey method and it was this method that was chosen for the cross-sectional GP survey. The option to complete an on-line electronic version of the questionnaire as an alternative to the traditional paper self-completion questionnaire was also offered to participants in an attempt to improve response from harder to reach groups of clinicians (for example locum doctors).

4.2.3 Advantages and disadvantages of postal questionnaires

Advantages

Postal questionnaires possess several advantages. Costs for undertaking a postal questionnaire survey are relatively low when compared to other methods of obtaining data. This is especially relevant if large numbers of participants are required or participants need to be recruited from either specific populations or from hard to reach geographical areas.

Postal questionnaires also have the practical benefits that they can be quick to perform, completed at a convenient time for the participant and can allow the participant ample time to complete the questionnaire. There are also methodological advantages for postal questionnaires. As postal questionnaires are self-completed, there is no interviewer bias and there are no interviewer effects, which makes them effective for sensitive subjects, as they create a certain amount of anonymity for the participant. [Rea and Parker 2005]

Disadvantages

Many of the disadvantages surrounding questionnaire surveys can be controlled and minimised given careful development of the questionnaire to be used. However questionnaires have clear and recognised disadvantages with the main disadvantage surrounding problems associated with bias. Bias in questionnaire surveys is a significant issue and is discussed specifically in Section 4.6 along with methods to try to limit bias in survey questionnaires.

Questionnaires often use fixed response answers or short open response answers. Whilst this can be an advantage, it can also be difficult to gauge the relevance and context of responses. Practical considerations include how to manage missing data or incomplete questionnaire responses as well as the recognition that sometimes questionnaires will not be completed and returned immediately, if ever, and so reminder methods to encourage response are recommended to minimise this. [Rea and Parker 2005]

The main disadvantage specifically relevant to postal questionnaires surrounds the administration burden that they create. Printing the relevant paperwork and address labels, envelope stuffing and sending the questionnaires out to participants can be a physically onerous and time consuming process, often involving large amounts of staff and resources to undertake. Additionally, large postal questionnaire surveys may require special arrangements with the postal services. Arrangement and processes also need to be in place to manage further mail outs and to manage returned questionnaires, including data extraction.

4.2.4 Sources of bias in survey methodology

Bias can be defined as:

> "*Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that differ systematically from the truth; deviation of results or inferences from the truth, or processes leading to deviation."* [bias. (n.d.)

Farlex Partner Medical Dictionary. (2012). Retrieved April 25 2016 from http://medical-dictionary.thefreedictionary.com/bias].

In survey research, bias can occur at many different stages. Choi and Pak(2005) categorized 48 different types of potential bias that can occur with questionnaire research relating to the design of individual questions, the way that the entire questionnaire is designed and the manner in which the questionnaire is delivered. [Choi and Pak 2005] Bias can also occur subsequent to data collection in the way that the data are analysed, interpreted and reported (reporting bias). [McGaura et al n 2010]

4.2.5 Questionnaire design

The aim of the study presented in this thesis is to investigate the current practice of general practitioners with regards to diagnosis, investigation and management of polymyalgia rheumatica and giant cell arteritis. A large representative population that is geographically diverse and accounts for all levels of clinical seniority and experience is ideally required to make robust conclusions from the data collected. Postal questionnaires are ideal for this purpose, as they specifically have the advantage of low cost, they can be performed quickly and large amounts of data from a wide, geographically diverse, targeted population can be obtained.

The questionnaires used however, have to be developed with care in order to limit bias and maximise the accuracy of the data being provided, whilst ensuring that the greatest possible response is achieved.

There are certain forms of bias that cannot be controlled for in survey questionnaires. These include false reporting (giving information that did not happen), social desirability issues (indicating what the participant thinks the right answers are, rather than what they actually do or think) and issues surrounding recall. [Choi and Pak 2005]

Bias and response rates can be influenced by questionnaire design. Methods for improving response rates are discussed in more detail in Section 4.9. To maximise the accuracy of the data, careful consideration of the overall design and format of the questionnaire has to be made. Each question needs careful construction to avoid ambiguity (by avoiding double barrelled questions, technical jargon and vague or inaccurate words). The accuracy of the data obtained from questionnaires is also dependent on the order of the questions (participants may learn in response to subsequent questions how they should have responded and may change answers) and the manner in which participants are able to answer the questions set. If participants are given a set of answers for a question to choose from then too few categories may cause participants to be forced into making a decision that they may not want to. Too many categories may lead to end aversion (not wanting to give the best or worst mark because it is at the end of the scale), response fatigue, and yes or no saying (ticking the same response whether accurate or inaccurate). [Choi and Pak 2005]

4.2.6 Survey response and non-response bias

The principal challenges of survey methods in order to make robust conclusions from data extracted from a completed survey are to ensure that the sample of participants that you

intend to survey is representative of the population as a whole and that this sampled population responds adequately.

If responders are significantly different from non-responders, then bias can occur. Significant effort therefore needs to be invested in ensuring that response rates are maximised.

Unfortunately levels of response are often used as a proxy indicator to judge whether or not the data is likely to be biased or not. Low response rates increase the risk of bias (although studies with a low response are not automatically biased), however studies where response is high may still be biased.

Studies will often compare baseline characteristics (e.g. age, gender, years of experience) between responders and non-responders to demonstrate that no differences exist between the groups and hence that no bias exists. However this does not necessarily guarantee the absence of bias, as Jenkins et al demonstrated in their questionnaire study on health status. Whilst two groups (initial responders and late responder) were identical in terms of baseline demographics, their responses to the specific questions were actually very different. [Jenkins et al 2004]

4.2.7 Response rates of questionnaires used in General Practice research

There is an increasing body of evidence that suggests that GPs are participating less and less in survey research and as such, response rates to surveys are declining despite employing evidence-based methods that have been demonstrated to improve response rates, for example reminder cards and further questionnaires or incentives (Section 4.2.10). [Creavin et al 2011] There has been some investigation into the reasons for this

declining participation in survey research and also much research into ways that survey response rates can be improved, both in commercial and medical survey research.

4.2.8 Characteristics of non-responders in surveys of general practitioners

Stocks and Gunnell (2000) investigated in depth, serial non-responders to postal surveys in the Avon area of the UK. They found that serial non-responders were likely to be older, were less likely to have a postgraduate degree and were less likely to be involved in undergraduate training. [Stocks and Gunnell 2000] This finding was confirmed by Hummers-Pradiera (2008) who also found that responders were more likely to be members of a Royal College. [Hummers-Pradiera et al 2008]. Bonevski (2011) found that responders in their study were more likely to be female and work part-time [Bonevski et al 2011] and finally Barclay (2002) found that non-UK graduates were a third less likely to respond to questionnaires, whilst UK graduates responded to surveys quicker if they were more recently qualified.[Barclay 2002] No correlation however has been demonstrated between response and measures of clinical care, such as the Quality and Outcomes Framework (QOF) score achieved by the practice. [Muller et al 2012] Unfortunately, survey non-responders have the potential to possess a wealth of knowledge and opinion that may be important and which could feasibly bias any conclusions made from a survey. Therefore, every effort has to be made to encourage potential participants to respond.

4.2.9 Why are people reluctant to take part in surveys?

Aldridge and Levine (2001) state several reasons why people are reluctant to take part in surveys.

These include choice, competition from other surveys, survey fatigue, intensification of social life, dislike of form filling and privacy. More and more individuals feel that it is their choice not to participate in surveys and it appears that there is an increasing trend to choose not to participate given that that response rates to surveys are declining. Because of the benefits of survey research as outlined above, surveys remain a popular methodology with more and more being conducted. Participants are likely therefore, to complete only surveys that they feel are relevant to them or that they are interested in. Associated with this is the impact on the probability of filling in future surveys given the amount of form filling that often accompanies questionnaires, which potentially could impact on the time, taken at work and at home becoming ever more limited. As a result surveys may be viewed as an intrusion of spare time affecting whether or not they are completed. The amount of paperwork that certain professions are required to undertake (healthcare professions being no exception) is ever increasing. Adding to this workload, especially if optional, is likely to reduce the chance of the questionnaire being completed. Finally, concerns over the use of personal data and opinions, have become an increasingly important problem. Surveys, even if completely anonymous may be viewed as an intrusion of privacy, impacting on a participant's decision to respond or not. [Aldridge and Levine 2001]

All of the points made above are also relevant to general practitioners, the target group for this research. Kaner (1998) followed up the non-responders to a postal questionnaire survey with a telephone interview to ascertain the reasons for their non-response. [Kaner et al 1998] The three most common reasons for non-response were:

1) Questionnaire was lost in pile of paperwork (24%)
2) Too busy to complete the questionnaire (21%)
3) I don't do any questionnaires (16%)

McAvoy and Kaner (1996) cited additional reasons for nonresponse including, the volume of questionnaires received, the length of the questionnaire, the time taken to participate in completing a questionnaire, resentment due to the interference that the questionnaire imposed, non-interest in the subject, issues surrounding confidentiality, disruption of workload, lack of provided information before completing the survey and lack of feedback offered. [McAvoy and Kaner 1996] These echo the general findings by Aldridge (2001) discussed above. By addressing the reasons why participants do not respond, surveys can be developed to maximise response. These methods are discussed in the following section.

4.2.10 Methods shown to improve response rate

Much research has been undertaken, particularly by those interested in commercial research, investigating ways to improve response rates to questionnaire surveys.

4.2.10.1 Questionnaire format

Length of questionnaire

As identified above, the length of questionnaire was an often cited reason for not responding to surveys. [McEvoy and Kaner 1996] This was supported by a Cochrane review by Edwards (2009) that showed that the odds of response was almost 75% higher with shorter questionnaires (although no optimal questionnaire length was offered).[Edwards et al 2009] Contrary to this, Grava-Gubins and Scott (2008) in their study on survey response amongst Canadian physicians, found no difference in response relative to length of questionnaire. [Grava-Gubins and Scott 2008] Nakash in their meta-analysis specifically relating to survey response in health care research found that shorter questionnaires improved response (OR 1.4, 95% CI 1.19 to 1.54). [Nakash et al 2006]

The length of questionnaire however, is highly dependent on the amount of information that is being sought or required to answer the research question, and although the optimal length of questionnaire is not known, data suggest that the length should be minimised to improve response. [Edwards et al 2009]

Appearance of questionnaire

Having a reputable university, organisational logo or sponsorship and a signed accompanying letter has been shown to improve response rates [Edwards et al 2002] yet other studies looking specifically at questionnaires for general practitioners found no effect on response rate when the survey was endorsed by a GP. [Bonevski et al 2011]

Coloured paper has not been shown to have any effect on response rates [Edwards et al 2002], although this seems quite surprising considering a common reason given for not responding is that the questionnaire had got lost in paperwork and presumably coloured paper would make it more identifiable. Font size used in survey questionnaires has been shown to improve response rates in older people and although paper thickness did not, it did improve completeness of the data collected. [Mallen et al 2008]

Delivery of questionnaire

Methods of delivery that have been shown to increase response rates include including stamped return envelopes, using brown envelopes, and using special delivery services and first class return of questionnaire. No differences in response rates have been shown with, different types of stamps, windowed envelopes or whether the questionnaire was sent to the participants work or home. [Edwards et al 2002]

4.2.10.2 Incentives

It is well recognised that incentives improve response rates whether they are gifts, monetary incentives or the chance to win a prize in a lottery. [Thomson et al 2004] The timing of when the incentive is given can also have an impact on response rates. In general, large monetary incentives appear to be the most effective at increasing odds of response (by up to a third). This can be further improved by enclosing the incentive with the questionnaire rather than giving it “if” the survey is completed. [Edwards et al 2002]

Specifically, when looking at response rates amongst GPs, small monetary incentives can boost response rates [Nakash et al 2006, Brealy et al 2007, Thorpe et al 2009], but the opportunity to win a large single prize has also been shown to be effective, particularly using champagne as the prize. [Thomson et al 2004] Despite incentives being a potential method of improving response, local research ethics committees are often reluctant to allow their use.

4.2.10.3 Relevance and interest in the subject

Several studies have shown that participants who are interested in the subject of the survey are more likely to respond. This has been highlighted in several investigations [McAvoy and Kaner 1996, Kaner et al 1998] with Edwards showing a doubling of odds of response in surveys with "more interesting questions." [Edwards et al 2002]

This aspect of survey research is difficult to control for, as it is difficult to predict what participants may be interested in and whether or not they would be interested in the research being conducted. Whilst selecting a cohort of interested participants may improve response rates and may for some studies be appropriate, it could have significant effects on any conclusions made. Uninterested participants represent a potentially important group that could yield important data, which if absent could introduce bias.

Table 4.2 summarises some of the literature investigating questionnaire response rates in medical research.

Table 4.2 Summary of research investigating questionnaire response rates

Lead Author	Aim	Study findings
Barclay 2002	To review of response rates from mailed questionnaires and the characteristics of non-responders	Non UK graduates less likely to respond compared to UK graduates RCGP members twice as likely to respond The more recent the qualification the faster the response
Bonevski 2011	To investigate strategies for improving response rates in surveys	Response rate overall 30.3% Higher proportion of responders are females and part time GPs No difference in response if the questionnaire is endorsed No difference in response with telephone reminder Preference of mode of questionnaire 81.1% postal 17.1 online 1.7% face to face 0.2% telephone
Brealey 2007	To investigate if monetary incentives improve response rates	Adjusted odds ratio of response 2.2 with a monetary incentive Speed of response was increased
Creavin 2011	To conduct a comprehensive review of primary care literature surrounding GP response rates to questionnaire surveys	Total average response rate 61% Higher mean response rate associated with journals in the higher quartile of impact factor. No evidence of increase in response rate between 2000 and 2009 despite the increased use of strategies to enhance response rate
Edwards 2002	To conduct a systematic review to determine the best methods of increasing response rates to postal questionnaires	Examples of methods to increase response rates: Monetary incentive (OR 2.02 95% CI 1.79 to 2.27 Short questionnaire (OR 1.86 95% CI 1.55 to 2.24) More interest in subject (OR 2.44 95% CI 1.99 to 3.01)
Grava-Gubins 2008	To assess the effects of various methodologic strategies on survey response rates	No difference between longer and shorter questionnaires No difference in mode of questionnaire delivery Monetary lottery incentive did not increase response

Lead Author	Aim	Study findings
Hummers-Pradiera 2008	To investigate the barriers to GPs' participation in primary health care research	Respondents more likely to have higher level vocational training More likely to be members of a college More likely to be involved in teaching medical students
Jones 1999	To compare postal, email and world wide web health survey methods	Email response rate 34% Postal 72%
Kaner 1998	To conduct a telephone survey of general practitioners' reasons for not participating in postal questionnaire surveys	Most common reasons for non-response: Questionnaire lost in pile of paperwork (24%) Too busy (21%) Don't do questionnaires (16%)
McAvoy 1996	To review general practice postal surveys	Reasons for non-response Volume of questionnaires Length of questionnaire Time taken to participate Resenting interference Uninterested in subject Issues surrounding confidentiality Disruption to work load Lack of information before hand Insufficient feed back
Nakash 2006	To conduct a systematic review on how to maximise responses to postal questionnaires	Impact of reminder systems (OR 3.71 95% CI 2.30 to 5.97) Shorter questionnaires (OR 1.35 95% CI 1.19 to 1.54) Incentive (OR 1.09 95% CI 0.94 to 1.27)
Stocks 2000	To determine the characteristics of general practitioners who routinely do not return postal questionnaires	Serial non responders are: Likely to be older Less likely to have a post graduate qualification Less likely to be involved in undergraduate training
Thorpe 2009	A review methods to improve response rates when surveying physicians	Improved response rates with: Dillman total design method[1] Personalised incentives Recorded delivery First class post

[a]OR: Odds ration [b]CI: Confidence interval

[1]Dillman total design method to maximise postal response: 1) Respondent friendly questionnaire 2) Total of 4 contacts using first class mail and a special contact for example registered post or telephone contact 3) Return envelope with a real stamp on it 4) Personalised documentation with each contact 5) Financial incentive to be included irrespective of whether the questionnaire is completed or not

4.2.10.4 Contact and communication

Covering letters outlining benefits to the sponsor or participant have not been shown to have any effect on response rates although indicating a benefit to society has a small impact on response but more significantly, assurances on confidentiality appear to have the greatest impact. [Edwards et al 2002] In addition, surveys with covering letters with a personalised approach with good quality explanatory information are likely to result in improved response rates. [Kaner et al 1998]

Pre-notification improved odds of response [Edwards et al 2002], but reminder systems have been shown to be the most effective method at increasing response rates to questionnaire surveys involving general practitioners (OR 3.71). [Nakash et al 2006]

4.3 Discussion

Although as highlighted above, a large Cochrane review was undertaken to explore how to improve response rates to postal questionnaires, [Edwards et al 2002] This review has its limitations, including the fact that only a few studies included are related specifically to medical settings and so its application in this area may be limited.

Medical questionnaires surrounding specific disorders such as PMR provide several challenges. There is a fine balance between the need for the data required to answer the research question and fulfil the aims of the research project with encouraging the participant to respond to the questionnaire and not making them feel tested or judged by the questions that are asked.

Interest in the subject is difficult to control for and there will always be a certain proportion of people that will not respond to surveys in which they have no interest. Additionally a certain proportion of potential participants, as a matter of routine, do not complete any surveys. [Kaner et al 1998] This is unfortunate as questionnaire surveys may be conducted in order to influence and improve health provision. Poor response however may lead to weakened conclusions, which may therefore have less influence. [McAvoy and Kaner 1996]

Addressing non-response remains a significant challenge in healthcare research as non-responders are a potentially significant source of important information and their views may have had a substantial impact on the overall study conclusions. For some investigations it may be practical to contact non-responders on an individual basis. For

most large scale surveys however, this is not feasible and as such the potential source of bias resulting from low response rates has to be acknowledged.

4.4 Development of the national GP PMR research survey

The following section describes the processes undertaken in developing the national GP PMR research survey. This section will review the application process for ethical approval, questionnaire design, obtaining contact details for potential participants and the practical aspects that need to be considered when conducting large scale surveys for example, mail-out, database development and data extraction processes.

4.4.1 Ethical Approval

Recent legislation has altered the process for ethical approval for studies that are undertaken involving health care professionals. As such ethical approval was sought from the Keele University Ethics Panel, rather than from the NHS National Research Ethics Service. [www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_126614.pdf]. Ethical approval was requested for a cross sectional survey of general practitioners and subsequently granted from the Keele University Ethics Review Panel on the 23rd of January 2012. [Appendix 3]

4.4.2 Questionnaire design

Using the evidence outlined above on improving response rates and the findings from the systematic review discussed in Chapter 3, a questionnaire was developed that built on findings from my previously published work examining GP management of PMR using the CiPCA dataset [Helliwell et al 2013] but also included relevant primary care related aspects from available national PMR guidelines. [Dasgupta et al 2010] This process is summarised in Appendix 4. The questionnaire underwent a process of review and refinement by relevant stakeholders (general practitioners, rheumatologists, PMR patients) for content and usability.

The final agreed questionnaire was eight pages long and endorsed with both Keele University and the Arthritis Research UK logos. Yellow paper was used (to reduce the risk of loss in a pile of paperwork) of 100g/m^2 thickness which has been shown to reduce the chance of missed pages and therefore increase the chance of a fully completed questionnaire. [Mallen et al 2008]

A single prize of a bottle of Dom Perignon champagne was offered as an incentive for completing the survey with all respondents being entered into a prize draw. Table 4.3 summarises the questions and domains of the questionnaire. The full questionnaire can be found in Appendix 3.

Table 4.3 Summary of questions and domains from the PMR National cross-sectional survey questionnaire

Domain	Question Number	Question theme
Diagnosis		
	1	Age at which the diagnosis of PMR would be excluded?
	2	Importance of key features
	3	Use of inflammatory markers
	4	Actions undertaken if inflammatory markers are normal
	5	Disorders routinely excluded before making a diagnosis
	6	Initial dose of prednisolone used
	7	Investigations routinely performed
Management		
	8	Action undertaken if response to treatment is poor
	9	Previous use of methylprednisolone
	10	Follow up of PMR patients
	11	Additional interventions or medications offered
	12	Indications for referral
	13	Management of relapse
	14	Impact on patients' lives
Challenges		
	15	Challenges of PMR diagnosis
	16	Challenges of PMR treatment
	17	General challenges associated with PMR
Giant cell arteritis (GCA)		
	18	Experience of managing GCA
	19	Symptoms indicative of GCA
	20	Signs indicative of GCA
	21	Management of suspected GCA
	22	Specialist to whom GCA patients routinely referred
	23	Initiating dose of prednisolone
Responder demographic questions		Age
		Gender
		Seniority
		Year of qualification
		List size
		Educational resources used

4.4.3 Sampling frame

The Binleys database [http://www.binleys.com/] was used as a sampling frame for this study. This large database contains the names and addresses of general practitioners working in the UK. In addition, it also contains other forms of information including the type of practice, the practice population size, practitioner seniority, and some of the clinical services that they provide. A random sample of 5000 general practitioners from across the United Kingdom (England, Wales, Scotland and Northern Ireland) was purchased. The data were imported into a specially created mailing database. The databases created for the PMR survey are described in more detail in the following section.

4.4.4 Database development for the PMR survey

Two databases were created specifically for this study. The first database was a mailing database and contained information from Binleys regarding the 5000 randomly selected general practitioners. This was used for the mail-out process described later. The second database contained the completed questionnaire response data.

4.4.5 On-line option for questionnaire completion.

To try and maximise questionnaire response, an on-line option was offered as an alternative method of questionnaire completion. Little research has been undertaken into the effectiveness of web based questionnaire methodology, especially when both

traditional postal and on-line options are offered in parallel. Whilst Hohwu (2013) suggested that internet questionnaire surveys are a promising and cost-effective method, when compared with postal questionnaires [Hohwu et al 2013], others have found that they are inferior in terms of response rate. [Leece et al 2004] However, Lusk (2007) found that an option to complete a survey online was in general favoured by younger males in particular. [Lusk et al 2007] The on-line version of the questionnaire was hosted by Survey Monkey [http://www.surveymonkey.com/]. This is a user-friendly and straight forward service, which provided the opportunity to test the questionnaire prior to it going 'live'. The online version also would not allow you to continue without completing each page and indicated to participants their progress through the questionnaire. Details of how to use this option were included on the covering letters and reminder card and could be accessed from the PMR survey home page. A unique study identification number was required in order to access the survey. Regular data up-dates were provided by Survey Monkey and imported onto the database created for participant questionnaire responses. Internet responses were specifically coded on the database.

The project also has a news webpage that participants and the general public are able to access should they wish to learn more about the study and its updates. [http://www.keele.ac.uk/pmr/gpstudy/news/]

4.4.6 Mail-out procedure

An initial survey pack containing a covering letter, study information leaflet, survey questionnaire and business return addressed envelope was sent to each of the randomly selected general practitioners. Non-responders were sent a reminder post card after two weeks, reminding them of the survey and also providing the website link to complete the questionnaire on-line if preferred. These documents can be reviewed in Appendix 3. After two weeks, non-responders were sent a further questionnaire and covering letter. This mail-out process has been shown to be effective at maximising the response rate in questionnaire surveys of health professionals. [Glidewell et al 2012]

The survey was open for a total of six weeks after the second survey pack had been sent out to non-responders.

4.5 Data Entry

Data were entered into the database designed specifically for the postal questionnaire. This was undertaken by administration staff trained in data entry. The data for every tenth questionnaire was reviewed by a second person to ensure quality control. Medical queries and uncertain entries were reviewed by TH when needed.

4.6 Data Analysis

4.6.1 Description of data obtained from the PMR National cross-sectional survey

Broadly the questionnaire survey contained two formats of questions, fixed /closed response questions (where participants would choose the option most appropriate for them) and open response questions that allowed participants to enter free text answers. Participants were given the opportunity for some fixed response questions to add free text as well. These different forms of data required different types of analysis methods and these will be described in the next sections.

4.6.2 Analysis of fixed response data

Simple descriptive statistics were generated using the statistical analysis package SPSS 22 [IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.], were used for the majority of the data obtained from the questionnaire. Response bias was assessed by comparing baseline characteristics of responders and non-responders provided in the original data requested from Binleys. This included number of partners in the the participants practice and the practice list size. For the majority of descriptive analyses, results will be presented as means, frequencies and percentages. Some questions asked participants to assign a graded importance of a sign, symptom or impact on life. These results are presented on radar plots of modal responses. Radar plots are an effective way to present and compare multiple values for multiple variables. The modal response was used as it conveys the most common response from participants. To investigate associations between respondent

characteristics and reported diagnosis and management strategies, logistic regression analyses were used.

4.6.3 Analysis of open response data

Open response questions can be challenging to analyse given that the range of responses can vary from just a few words to long, extended paragraphs. Two common methods of analysing this type of data are content analysis and thematic analysis. Thematic analysis is discussed in detail in Chapter 6, as this method will be used to analyse the qualitative GP interviews that form the second half of this thesis.

4.6.3 Content Analysis

Krippendorf (1989) defined content analysis as "*A research technique for making replicable and valid inferences from data to their context*." [Krippendorff 1989 p403] At its most basic level it is a method of analysis that involves assessing the occurrence and frequency of a subject of interest within the available data. This may be something as simple as a single word but can be more complex involving general themes or processes.

Thematic content analysis goes beyond analysing the simple frequencies of events of interest by developing themes from emerging the data. This method allows both representations of the impact of a particular issue (using simple frequencies) but also an element of superficial interpretation of text with subsequent development of simple categories to create global themes. [Krippendorf 1989]

4.6.4 Content analysis versus thematic analysis

Content analysis has its origins as a quantitative research method and was principally developed for use in media research. However qualitative approaches have been used and developed for other areas of research including medicine and psychology, allowing the interpretation of data as well as calculating the actual frequency of an issue or subject. [Krippendorf 1989, Vaismoradi et al 2013] Issues remain over some of the concepts of qualitative content analysis [Graneheim and Lundman 2004, Vaismoradi et al 2013] and its comparisons with thematic analysis. Table 4.4 summarises the different approach to analysis with these two methods. Quotes from the open responses are labelled with the participants' anonymised survey identification number, their age, length of time practising as a GP, their gender and their seniority/role.

Table 4.4 Comparisons between thematic analysis and content analysis

Thematic Analysis [Braun and Clarke 2006]	**Content Analysis [Elo and Kyngas 2008]**
Familiarisation with the data Immersion in the data by transcription, reading and re-reading in an "active" way to search for patterns and meaning.	*Preparation* Immersion in the data, making sense of it as a whole and deciding upon the what will be analysed
Generating initial codes Creating codes that relate to features in the data that are interesting and grouping data that is relevant to each code.	*Organising* Data analysis by content, development of codes and grouping of codes to create categories and sub-categories
Searching for themes Grouping codes to develop general themes	
Reviewing themes Re-assessing the identified themes to ensure that they are supported by the data	
Defining and naming themes The final detailed analysis and review of each theme and its story. How do the identified themes relate to each other and does the data support this.	
Producing the report Final analysis and overall presentation of the data in a final report	*Reporting* Reporting the analytical process, the results of that process and the overarching story that emerges from the data

4.7 Summary

A key difference between a thematic approach and content analysis lies in the type of data resulting from the open response questions. Thematic analysis usually requires a certain level of interpretation of in depth and detailed data that is often obtained from a limited number of individuals. Emerging themes are not usually quantifiable but are something important that is deemed to relate to the overall research question. In content analysis a theme may develop simply as a result of the frequency of its occurrence in the data. Additionally, owing to the limited length of responses in the

survey and therefore, the lack of overall context of the response, the amount of interpretation that can be made is limited, unlike for example thematic analysis of in-depth interviews.

A thematic content analysis was therefore chosen to analyse the open response data given the number of responders and the brevity and often superficial detail of which the open response data consists. The importance of each emerging theme can be assessed quantitatively in relation to the frequency with which that the theme occurs. NVivo is software package often used for analysing qualitative data [NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 10, 2012]. It allows data to be coded into themes. NVivo 10 was used to analyse the open response data by allocating responses into relevant categories.

4.8 Conclusions

This chapter summarises and justifies the methods used in developing the national PMR questionnaire survey of GPs along with the strengths and limitations of the approach used. The analysis methods used for the quantitative survey and the methods used for the free text part of the survey are also described. The following chapter describes the results of the data obtained from the survey

Chapter 5: PMR National Cross-sectional Survey: Results

5.1 Introduction

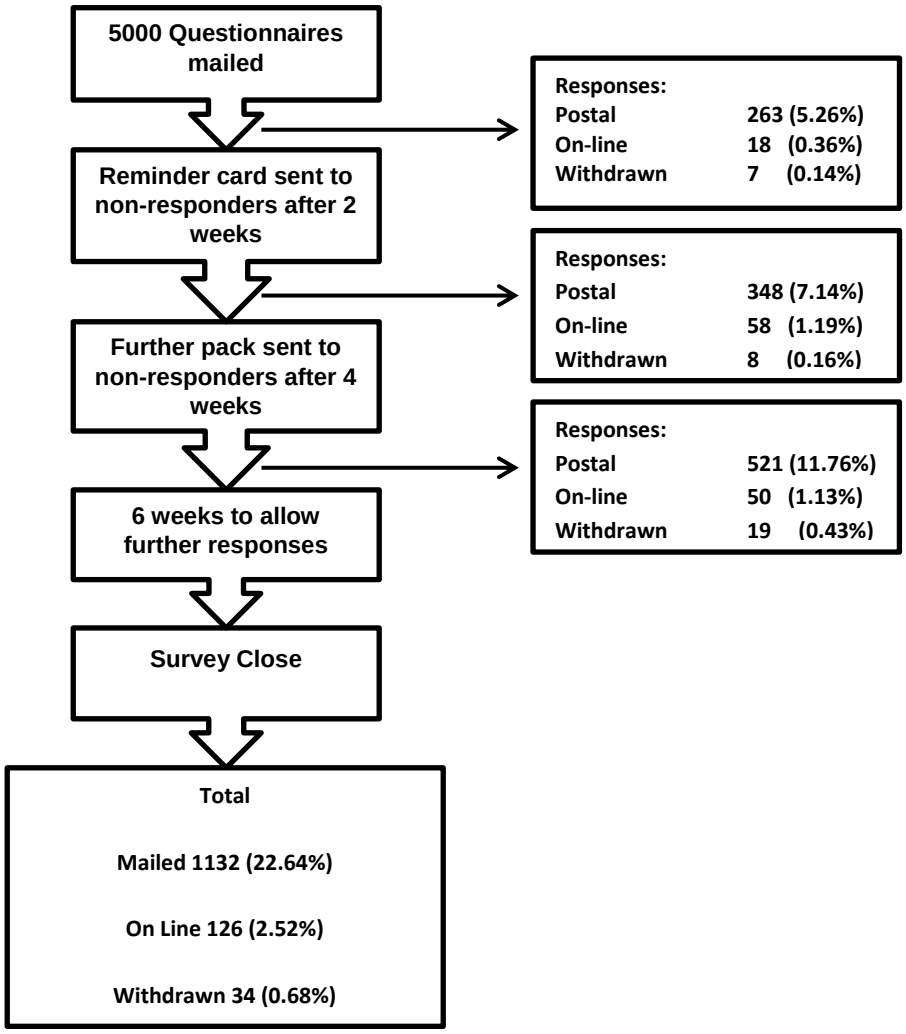
This chapter presents the results from the national PMR GP cross sectional survey, the methodology of which is described in detail in Chapter 4. The postal questionnaire included fixed and open response questions around GPs' diagnosis and management of PMR, both of which are presented in this chapter under headings focusing on the diagnosis (Section 5.3), management (section 5.4), impact and challenges (Section 5.5) associated with PMR in primary care. Each section of results references the related question(s) from the survey questionnaire. First the characteristics of responders and non-responders are compared.

5.2 Response and baseline characteristics of responders

5000 questionnaires were mailed to potentially eligible participants, and 1258 (25.2%) completed questionnaires were received. Nine responses were found to be duplicates resulting in 1249 (25.0%) unique, completed questionnaires for use in analyses

Figure 5.1 presents the response rates at selected points of the questionnaire mail-out process, the proportion of participants completing the questionnaire on-line and those withdrawing from the study at each stage.

Figure 5.1 Survey flow and questionnaire response



***** It was found on data cleaning that some respondents had completed both paper and electronic questionnaires. The response with most questions answered therefore was chosen to be included for analysis. 8 of the duplicates that were removed were completed on-line.

Of those responding 1132 (90.63%) completed a paper questionnaire and 126 (10.07%) completed the on-line version. The majority of responders were GP partners, with the mean duration of qualification being 13.4 years. The baseline characteristics of responders and the available characteristics (obtained from Binleys initial data supply) of non-responders are presented in Table 5.1.

Table 5.1 Baseline characteristics of responders and non-responders to the PMR National cross-sectional survey questionnaire

Characteristic	Overall responders n=1249	Postal responders n=1132	Online responders n=123	Non-responders n=3749
List size (Median, IQR)	7129 (6463,5500)	7098 (6375,5500)	7519 (7000,5175)	6574 (5700,3600)
Number of partners (Median, IQR)	3.78 (4,3)	3.76 (4,3)	4.02 (4, 3)	3.24 (3, 4)
Age (year) (Mean, SD)	44.05 (9.25)	44.48 (9.45)	40.8 (7.73)	n/a
Female (n, %)	649 (52)	598 (53)	68 (55)	n/a
Seniority (n, %)				n/a
Senior partner	172 (13.8)	165 (14.7)	7 (5.7)	n/a
Partner	757 (60.6)	673 (59.8)	83 (67.5)	n/a
Salaried	260 (20.8)	234 (20.8)	26 (21.1)	n/a
Locum	31 (2.5)	29 (2.6)	2 (1.6)	n/a
Years qualified as a doctor (Median, IQR)	20.1 (18,15)	20.4 (18, 24)	16.3 (15,9)	n/a
Years qualified as a GP (Median, IQR)	13.5 (11,14)	13.8 (11, 15)	9.5 (15,9)	n/a

SD – standard deviation; IQR – interquartile range, n/a – not available

The mean age of survey postal responders was 44 years, which is lower than the national mean GP age of 47 years. 73.8% of responders were GP partners which is comparable to the UK national demographic where 75.7% of GPs are partners [GP Data HSCIC (Health and Social Care Information Centre)]. Study participants were more likely to work in slightly larger practices. Additionally they worked in practices with more GP partners when compared to non-responders.

The regional variation in response is illustrated in Table 5.2.

Table 5.2 Regional variation in questionnaire response

Region	Mailed		Responders		
	n	% of total	n	% of all responders	% of baseline
London	793	15.9	139	10.8	17.5
Midlands & Eastern	1197	23.9	296	23.0	24.7
North	1265	25.3	325	25.2	25.7
Northern Ireland	21	0.4	6	0.5	28.6
Scotland	500	10.0	141	10.9	28.2
South	964	19.3	322	25.0	33.4
Wales	260	5.2	60	4.6	23.1

The region with the highest response was the South of the UK, whilst London had the poorest response.

5.3 Diagnosis

This section presents the results focusing on making an accurate diagnosis of PMR. The following section summarises the fixed response data.

5.3.1 Age (Question 1)

Table 5.3 summarises the ages below which GPs would exclude the possibility of PMR. The findings from the survey suggest that GPs would not necessarily exclude PMR based solely on age, although the majority of GPs (72.5%) would appropriately exclude PMR in patients under the age of 50 years.

Table 5.3. Age below which PMR would be excluded

Age Category (years)	n	(%)
Less than 30	208	(16.7)
Less than 40	264	(21.1)
Less than 50	434	(34.7)
Less than 60	156	(12.5)
Less than 70	102	(8.2)

5.3.2 Use of investigations

5.3.2.1 Inflammatory markers (Question 3)

Raised inflammatory markers support a diagnosis of PMR. The majority of respondents (n=1118 (89.5%)) reported checking the erythrocyte sedimentation rate (ESR) whilst 683 respondents (54.7%) routinely request C-reactive protein (CRP). Table 5.4 illustrates the actions of responding GPs in cases where inflammatory markers are normal. 392 (31.4%) report that they would refer such patients for specialist review, whilst a quarter of responders (25.2%) reported that they would exclude a diagnosis of PMR. Half of respondents (50.7%) stated that they would consider a trial of treatment.

Table 5.4 Actions taken in suspected PMR when inflammatory markers are normal

Action taken	n *	(%) *
Exclude PMR as potential diagnosis	315	(35.2)
Recheck bloods	468	(37.5)
Refer to specialist	392	(31.4)
Offer treatment trial	633	(50.7)
Other	101	(8.1)

*Participants were not limited in the number of boxes that could be checked and so totals are greater than the number of participants and percentages add up to greater than 100

Responses from the open response questions highlight that diagnosing PMR in the context of normal inflammatory markers was a challenge. Respondents suggested that the overall clinical context relating to clinical presentation, signs, symptoms and investigation results had to be considered, although it was highlighted that normal inflammatory markers did make the diagnosis of PMR less likely, resulting in GPs more actively considering alternative and differential diagnoses.

> *"basically care would be individual, if history was highly suggestive of PMR, patient 60 who is not diabetic or osteopenic where steroid treatment could help I would be happy to go ahead and treat, if more complex may seek second opinion"* **Participant 1665 (11, F, P)**

Key: [time qualified as a GP (years), gender (male/Female), seniority/role (S:salaried, L:locum, P:partner, SP: senior partner)]

5.3.2.2 Other blood tests (Question 6)

Whilst inflammatory markers (97.8%) and full blood count (95.9%) are almost universally performed, other recommended screening investigations were not routinely undertaken. The investigations reported to be routinely undertaken by participating GPs are illustrated in Table 5.5

Table 5.5 Investigations routinely undertaken by GPs

Investigation	**GP undertaking the investigation routinely**	
	n	**%**
Full blood count (FBC)	1198	95.9
Erythrocyte sedimentation rate/c-reactive protein (ESR/CRP)	1222	97.8
Rheumatoid factor (RhF)	730	58.6
Glucose	520	41.6
Anti-nuclear antibodies (ANA)	412	33.0
Urea and electrolytes (U&E)	866	69.3
Creatinine Kinase (CK)	579	46.4
Liver function tests (LFT)	806	64.5
Thyroid function tests (TFT)	801	64.1
Bone	670	53.6
Serum electrophoresis	250	20.0
Bence Jones protein	211	16.9
Anti-cyclic citrullinated peptide antibody (Anti CCP)	99	7.9
Prostate specific antigen (PSA)	137	11.0
X-Ray	161	12.9
Ultra sound scan (USS)	22	1.8
Other Imaging	18	1.4
Urinalysis	195	15.6
None	5	0.4
Other	30	2.4

Plasma viscosity was a commonly indicated “other” investigation and its use appears to be largely dependent on regional availability of inflammatory markers and local clinical guidance.

5.3.3 Exclusion of PMR differential diagnoses (Question 5)

The majority of responders reported that they actively try to exclude giant cell arteritis (GCA) when diagnosing PMR (80.1%). However exclusion of other causes for symptoms was not routine (Table 5.6). In particular, only 66.3% of respondents reported routinely excluding infections, and only 54.6% reported routinely trying to exclude malignancy.

Table 5.6 Routine exclusion of disorders that can mimic PMR

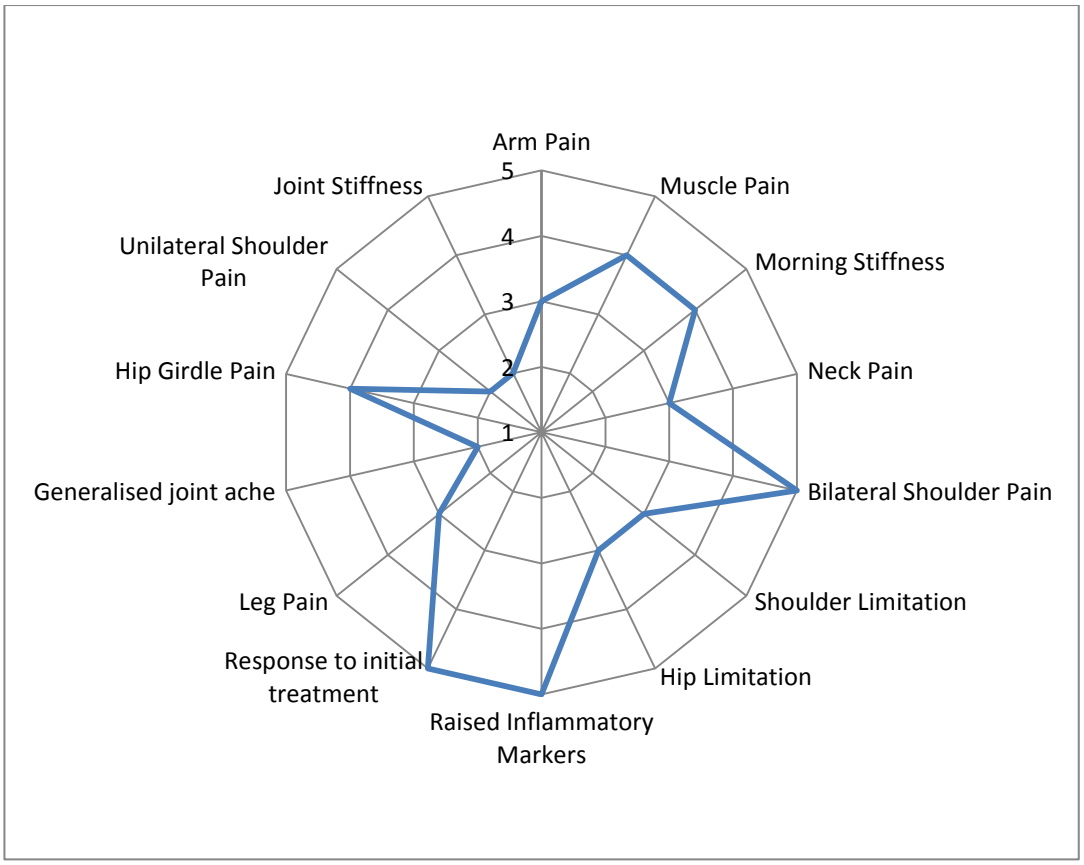
Disorder	n	(%)
Giant Cell Arteritis	1001	(80.1)
Rheumatoid arthritis	864	(69.2)
Active infection	828	(66.3)
Drug induced myalgia	814	(65.2)
Relevant rheumatological disorders	759	(60.8)
Osteoarthritis	745	(59.6)
Malignancy	682	(54.6)
Relevant endocrine disorders	348	(27.9)
Relevant neurological disorders	285	(22.8)

5.3.4 Clinical features (Question 2)

Participants were asked to rate the importance of selected clinical features associated with PMR from a provided list that was generated from the literature review presented in Chapter 3 (some of which were typical of PMR and others that were atypical). Participants were asked to rate the importance of each feature between one and five with five being “highly important” and one the “least important”. The median score for each feature was calculated with the results illustrated in Figure 5.2.

Bilateral shoulder pain, raised inflammatory markers and response to treatment were rated as the most important features in diagnosing PMR, with muscle pain, morning stiffness and hip girdle pain as additional important features.

Figure 5.2. Radar plot depicting median scores relating to participant rating of importance of presenting clinical features used to diagnose PMR



5.3.4.1 Open response questions to symptoms used for identifying PMR (Question 2)

As well as rating the listed features offered in the questionnaire, participants were offered the opportunity to add other features they felt were important in identifying PMR. These are summarised in Table 5.7.

Table 5.7 Content analysis of open responses of presenting features of PMR

Category	Theme Count
Constitutional Symptoms	89
Symptoms of GCA	28
Reduced mobility	20
Muscle weakness	19
Muscle joint aches	18
Depression/low mood	16
Overall global picture	14
Muscle tenderness	7
Other	3

General constitutional symptoms, (including fatigue, tiredness and lethargy) was the main theme that emerged from the free text content analysis. Fatigue was the predominant feature highlighted. Weakness reported as both generalised and muscular was another feature reported by some GPs although there was no indication as to whether this was objective or subjective weakness. Some respondents also suggested that it is more the overall global assessment that is important and the combination of signs, symptoms and investigation findings, rather than individual components in diagnosing or excluding PMR.

5.3.4 Analysis of responder characteristics and associations with guideline appropriate diagnosis (Question 5)

UK Clinical guidelines recommend excluding a range of conditions prior to diagnosing PMR. [Dasgupta et al 2010] These include the exclusion of GCA, active infection and cancer as a cause for the symptoms. Logistic regression analysis was undertaken to determine the characteristics of responders (experience measured by years since qualification, gender and the use of medical information resources) who were less likely

to undertake these recommended steps. No significant associations were found that identified a particular group that were not undertaking appropriate exclusions.

5.3.6 Challenges surrounding the diagnosis of PMR (Question 14)

Three general themes were identified surrounding challenges related to diagnosis. These included atypical presentations, overall uncertainty and other issues regarding diagnosis. These are summarised in Table 5.8.

Table 5.8 Results of thematic content analysis of open response question relating to challenges surrounding diagnosis

Category	Theme Count
Normal Inflammatory markers	284
Possible mimicking disorders	183
Diagnostic uncertainty/fear of misdiagnosis	112
Non-specific presentation	108
Atypical presentation	87
Co / multi-morbidity	55
Poor initial treatment response	50
Long term glucocorticoid use	32
No Challenges	24
Giant cell arteritis	24
Lack of diagnostic gold test	22

5.3.6.1 Atypical Presentation

This theme relates to the varying symptoms, signs and features with which patients suspected of having PMR first present. Classically symptoms include bilateral shoulder pain and/ or hip girdle pain, morning stiffness and muscle aches with raised inflammatory markers. However, patients often do not present like this, and it is the less typical presentations that cause diagnostic difficulty.

"Diagnosis often more difficult than the text book suggests, would love to always have patients that report classical symptoms and have elevated inflammatory markers and respond well to treatment, this happens rarely"

Participant 3063 (29, M, SP)

Atypical presentations can vary from abnormal distributions of symptoms to unusual joint involvement and can be made more challenging as it can be difficult for patients to express exactly the type and character of pain or stiffness. This is especially difficult for patients with illnesses such as dementia which has an increasing prevalence with increasing age.

"Dementia patients and PMR, uncertainty re history, sought advice from secondary care"

Participant 2378 (9, F, S)

Atypical presentations also include situations where a patient may have typical features of PMR but without confirmatory raised inflammatory markers. As illustrated in Table 5.8, normal inflammatory markers were the most commonly quoted factor contributing to diagnostic uncertainty.

"Typical symptoms but normal ESR would make me under confident to diagnose and may result in a referral to rheumatology. A rheumatologist diagnosed one of

my patients as above and I felt happy to treat with steroids with a normal ESR"

Participant 3174 (7, F, P)

5.3.6.2 Uncertainty of diagnosis

General uncertainty and fear of misdiagnosis was a common issue expressed by responders but whilst an atypical presentation may be one element contributing to diagnostic uncertainty there were other specific areas where for PMR, diagnosis was reported to be difficult. PMR has an extensive differential diagnosis with many disorders that can present clinically in a similar way, and as there is no gold standard diagnostic test for PMR it can be very difficult to separate PMR from mimicking disorders.

"there is no diagnostic test so it's a clinical diagnosis with suggestive blood results which can be hard to feel certain about and hard to convey convincingly to the patient, also there being lots of other conditions with similar presentations makes this even harder"

Participant 4814 (2, F, S)

A significant response to glucocorticoid treatment is a well-recognised feature of PMR although its usefulness in classification criteria has been recently challenged. [Dasgupta et al 2012] As such this feature was often used to confirm the diagnosis by participants. However, when response to treatment was suboptimal, it caused uncertainty.

"Classic presentation, raised ESR but no response to steroids - actually had metastatic cancer"

Participant 1029 (2, M, P)

Finally respondents reported the non-specific way in which PMR can present to be especially difficult. This was particularly thought to be a problem in older patients with comorbidity where pre-existing symptoms could confuse the clinical picture.

"often symptoms in older patients with multiple co-morbidities, difficult sometimes to distinguish between any related symptoms including osteoarthritis and fibromyalgia"

Participant 1955 (17, F, P)

5.3.6.3 Other diagnosis themes identified

This theme encompasses those areas of diagnosis that whilst expressed less frequently than the above themes, may represent important aspects that need considering. These include the difficulties in making a diagnosis where there is the possibility of an inter-current illness, which may be accounting for the raised inflammatory markers.

"inter-current illness (chest infection) confusing inflammatory marker interpretation"

Participant 1922 (5, F, P)

Additional challenges expressed included the problem that PMR is relatively unusual and depends on the practice population, and role of the individual GP. Exposure to PMR can be very dependent on the demographic of the practice population which will impact on the relative experience of an individual GP and therefore the confidence in diagnosing and managing it.

> *"I have not seen many patients with PMR I work mainly in a practice for homeless people which is a younger population and as an academic GP, maybe I'm missing some diagnoses"*
>
> **Participant 3106 (8, M, L)**

Finally there is sometimes difficulty in patients accepting the diagnosis or uncertainty amongst patients who are concerned they may have a different diagnosis.

> *"often getting patients to accept diagnosis and the need for steroid treatment…. coming to terms with diagnosis, addressing secondary depression"*
>
> **Participant 1588 (7, M, P)**

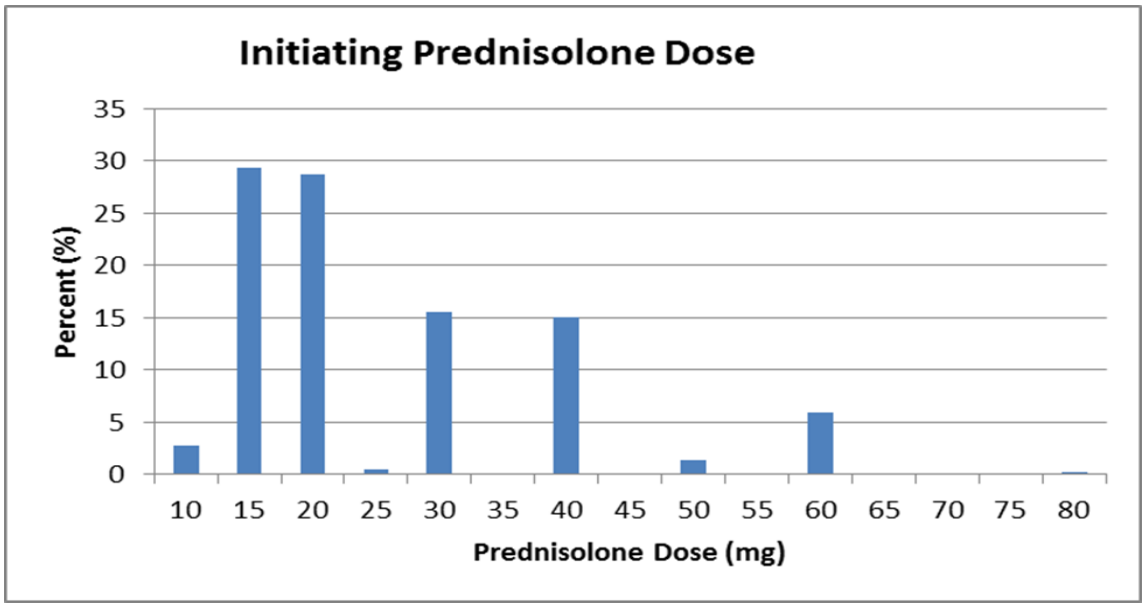
5.4 Management of PMR

The following section focuses on the treatment and management of PMR with a specific focus on prednisolone dosing and the management of the potential adverse effects of long term treatment with glucocorticoids.

5.4.1 Initial Treatment (Question 6)

UK National guidelines suggest an initial dose of 15mg of prednisolone [Dasgupta et al 2010] for managing PMR followed by a gradual dose tapering. The median initiating dose of prednisolone was found to be 20mg with a most frequent initiating dose of 15mg (Figure 5.3). 704 (56.4%) responders would initially treat PMR as per guideline recommendation with either 15mg or 20mg of prednisolone. Three further dosing peaks are noted with a starting dose of 30mg, 40mg and 60mg of prednisolone.

Figure 5.3 Initiating prednisolone dose (mg)



373 (29.9%) responders would exclude PMR as a diagnosis based on a poor response to glucocorticoids, although the majority (68.4%) would consider specialist referral in this scenario. Two main themes emerged from a review of the open response question related to this topic. First, a poor response to initial treatment would lead to consideration of an alternative diagnosis rather than completely excluding PMR. This is also dependant on the confidence the general practitioner had in the initial clinical presentation. Second, a poor treatment response would prompt additional investigation, further reviewing of patients and consideration of a referral for specialist review.

> *"depends on clinical context. If my suspicion was high I would seek specialist advice. If lower index of suspicion, I'd probably exclude PMR and cast round for alternative explanations (which may also include referral depending on context) perhaps by casting a wider investigative net."*
>
> **Participant 1132 (17, M, P)**

Some responders indicated that they would try physiotherapy and/or alternative medications such as anti-inflammatories or analgesics to improve symptom control. Stopping treatment with prednisolone in situations of poor response however was a common theme in the open response questions, although some responders indicated that they would increase the dose of prednisolone and one responder indicated they would do this to a maximum of 60mg.

Intramuscular methylprednisolone is an alternative treatment option to oral prednisolone but was not commonly used amongst responders. 54 responders (4.4%) reported that they had used it to treat PMR. In general, responders who had used methylprednisolone found that patients had a good response to treatment.

> *"patient reports excellent resolution of disabling symptoms"*
>
> **Participant 382 (23, F, P)**

A common theme in those that had experience of treating PMR with methylprednisolone was that it was usually administered after gaining advice from specialists.

> *"therapeutic trial [of methylprednisolone] on one occasion in someone without raised ESR, that rheumatologist felt had PMR - wouldn't use routinely"*
>
> **Participant 991 (23, F, P)**

5.4.2 Long term management and monitoring of PMR patients

Long term follow up of PMR patients is usually conducted in primary care. This involves glucocorticoid dose tapering and focused assessments for the development of GCA, potential other mimicking disorders and adverse effects of treatment (for example osteoporosis and diabetes).

5.4.2.1 Adjuvant Treatment (Question 10)

As discussed in Chapter 1, osteoporosis prophylaxis in the form of calcium and vitamin D supplements, and bisphosphonates (if indicated) is advised for PMR patients being treated with long term glucocorticoids [Dasgupta et al 2010]. Current guidance does not advocate the use of routine gastric protection, but should be considered in at risk groups, (for example previous peptic ulcer disease or patients taking other medications (for example aspirin) that may increase the risk peptic ulceration) as gastric symptoms are a common adverse effect in patients taking low to medium dose glucocorticoids. [Hoes et al 2009] Survey findings are illustrated in Table 5.9 and suggest that the majority of respondents routinely offer bone protection including calcium supplements and bisphosphonates (81.3%) and that gastric protection is also commonly offered (68.9%).

Table 5.9 Summary of the results surrounding the long-term management and follow up of PMR

Adjunctive therapy routinely offered to PMR patients	n	(%)
Routinely offer bone protection	1016	81.3
Routinely offer gastric protection	860	68.9
Routinely offer analgesia	688	55.1
Routinely offer physiotherapy	177	14.2
Routinely offer alternative therapies	66	5.3
Routinely offer referral to secondary care	149	11.9
Routinely offer joint injection	19	1.5
Routinely offer information leaflet	757	60.6
Routinely offer website information	356	28.5
Routinely offer support group	84	6.7
Routinely offer none	8	0.6
Routinely offer non-steroidal anti inflammatory	29	2.3

A review of the responses to the open question relating to this topic indicated that participants sometimes offered alternative therapies to help treat PMR. This most often involved a referral for a course of acupuncture, but other respondents indicated that hydrotherapy and aromatherapy were other alternatives.

5.4.2.2 Indications for specialist review (Question 11)

The most common reasons cited by respondents for referral for specialist review were diagnostic uncertainty (87.1%) and poor response to treatment (79.3%). 6.4% of respondents indicated that they referred all PMR patients to secondary care as a matter of routine. These results are summarised in Table 5.10

Table 5.10 Indications for referral for specialist review

Indications for referral for specialist review	n	(%)
Diagnostic uncertainty	1088	87.1
Poor response to treatment with glucocorticoids	991	79.3
Request of patient	554	44.4
Young patients	543	43.5
Medication complications	446	35.7
Normal inflammatory markers	399	31.9

5.4.2.3 Management of PMR flares (Question 12)

PMR symptoms may at any time flare up. The most common course of action in the case of a PMR flare was to recheck inflammatory markers (72.5%), whilst 46.4% of responders reported increasing glucocorticoids to the previously effective dose and 62.6% increasing dose until symptoms were controlled. The full results from this question are illustrated in Table 5.11

Table 5.11 Management of PMR flares

Action undertaken to manage a PMR symptom flare	n	(%)
Increase glucocorticoid until symptoms controlled	777	62.2
Recheck inflammatory markers	906	72.5
Increase glucocorticoid only if ESR raised	199	15.9
Increase glucocorticoid by 5mg	144	11.5
Increase glucocorticoid even if ESR normal	265	21.2
Refer to secondary care	209	16.7
Increase glucocorticoid to previous effective dose	579	46.4

5.4.3 Challenges experienced when managing PMR patients (Question 15)

The open question identified a number of challenges related to treatment in the management of PMR (Table 5.12), which are discussed in turn below.

Table 5.12 Frequency of challenges regarding PMR treatment

Category	Theme Count
Prednisolone titration and reduction	295
Glucocorticoid adverse events	285
Symptom relapse	111
Overall duration of treatment	89
Adjuvant medication	85
Stopping steroids	63
Poor response to initial treatment	63
Comorbidity and polypharmacy	58
Compliance to treatment	55
Regular monitoring	30
Initiating dose of prednisolone	27
Patient self -reducing medications too quickly	14

5.4.3.1 Challenges of long-term treatment with glucocorticoids

The predominant theme relating to treatment challenges surrounded the use and potential adverse-effects of glucocorticoids. Some responders expressed issues surrounding unclear advice on initiating doses of prednisolone as well as treatment tapering which was reported as an area of considerable challenge for GPs treating PMR, and for patients given the potential for adverse effects balanced against the fear of symptom recurrence.

> *"Main challenge is coming off steroids most patients are completely delighted when their symptoms resolve after a week on steroids but become despondent and anxious when they start to experience steroid side effects (e.g. weight gain) and discover when they try to step down off their steroids their symptoms re-occur"*
>
> **Participant 1665 (11, F, P)**

Compliance with treatment was a notable issue for GPs responding to the survey and for patients with PMR this was related to both over treatment and adhering to dose reduction regimens.

> *"frequent input with steroid regimes/doses especially when they struggled with dose reduction, no matter how slowly it was done - some patients feel dependent on steroids and will end up taking more (without consulting you) to control symptoms even when perhaps their symptoms might not be due to PMR"*
>
> **Participant 818 (4, M, P)**

Finally, stopping treatment was reported to be challenging for both physical and psychological reasons.

> *"those difficult to wean off - seem to become physically or psychologically dependent on steroids"*
>
> **Participant 1228 (21, M, SP)**

5.4.3.2 Co/multimorbidity and multi-pharmacy

The second theme identified from the free text responses relates to the impact that PMR treatment has on other illnesses, interactions with existing medications and the need in some cases to try and prevent any potential side effects and complications of long term glucocorticoid treatment.

> *"Main problems are with anticoagulated patients (dabigatran will help) and patients with osteoporosis, heart failure, frailty, renal failure etc."*
>
> **Participant 253 (17, M, S)**

Glucocorticoid treatment was also noted to impact on PMR patients other comorbidities which tend to be more common in older age groups. Diabetes was the predominant illness being reported to be affected by PMR treatment.

"one patient was diabetic and blood sugar control with oral steroids was a challenge"

Participant 3849 (11, F, S)

Treatment for PMR also involves the consideration of the prevention of potential adverse effects associated with long term glucocorticoids. This in itself can present challenges with respect to multi-pharmacy and compliance.

"*complicated meds regime with need for bone prophylaxis and PPI as well as steroids"*

Participant 2227 (9, F, P)

"*having to take bone protection as well tolerating it"*

Participant 4756 (12, F, S)

5.4.3.3 Practicalities of treatment and other challenges

The final theme surrounds the practicalities of treating PMR and other challenges which although not frequently cited pose interesting challenges that are worthy of further consideration. The following quotes give some examples of the type of practical issues that GPs reported.

> "*keeping follow up and reduction in steroids - not enough appointments to bring back routinely patient need to be aware of plan and proactive if arranging tests and symptoms review"*
>
> **Participant 3529 (5, F, S)**

> "*practicalities adjusting dosette boxes which are prepared few weeks ahead with need to change steroid dose regularly"*
>
> **Participant 211 (8, F, S)**

> "*often housebound and no easy mechanism for review"*
>
> **Participant 3558 (17, F, P)**

5.5 General challenges surrounding PMR (Question 16)

The final open question explored any further or general challenges experienced by GPs that were not associated with diagnosis or management. Table 5.13 shows the frequency of the various categories from the data relevant to this question. Diagnosis and treatment with glucocorticoids were still identified as the predominant challenges expressed for this question and have been discussed in detail already, whilst giant cell arteritis will be discussed in Chapter 7. Other themes not already identified will be discussed in this section in more detail.

Table 5.13 Other challenges of PMR in primary care

Category	Theme Count
Diagnosis	467
Treatment with glucocorticoids	265
Follow up and monitoring	111
Chronic condition	43
Relapse and flare	39
Few or none	39
Multi-morbidity and polypharmacy	25
Giant cell arteritis	21
Access to specialists	17
Lack of guidance	11

The third predominant category after diagnosis and treatment surrounded the practical issues associated with follow up, monitoring and the pressure on availability of appointments.

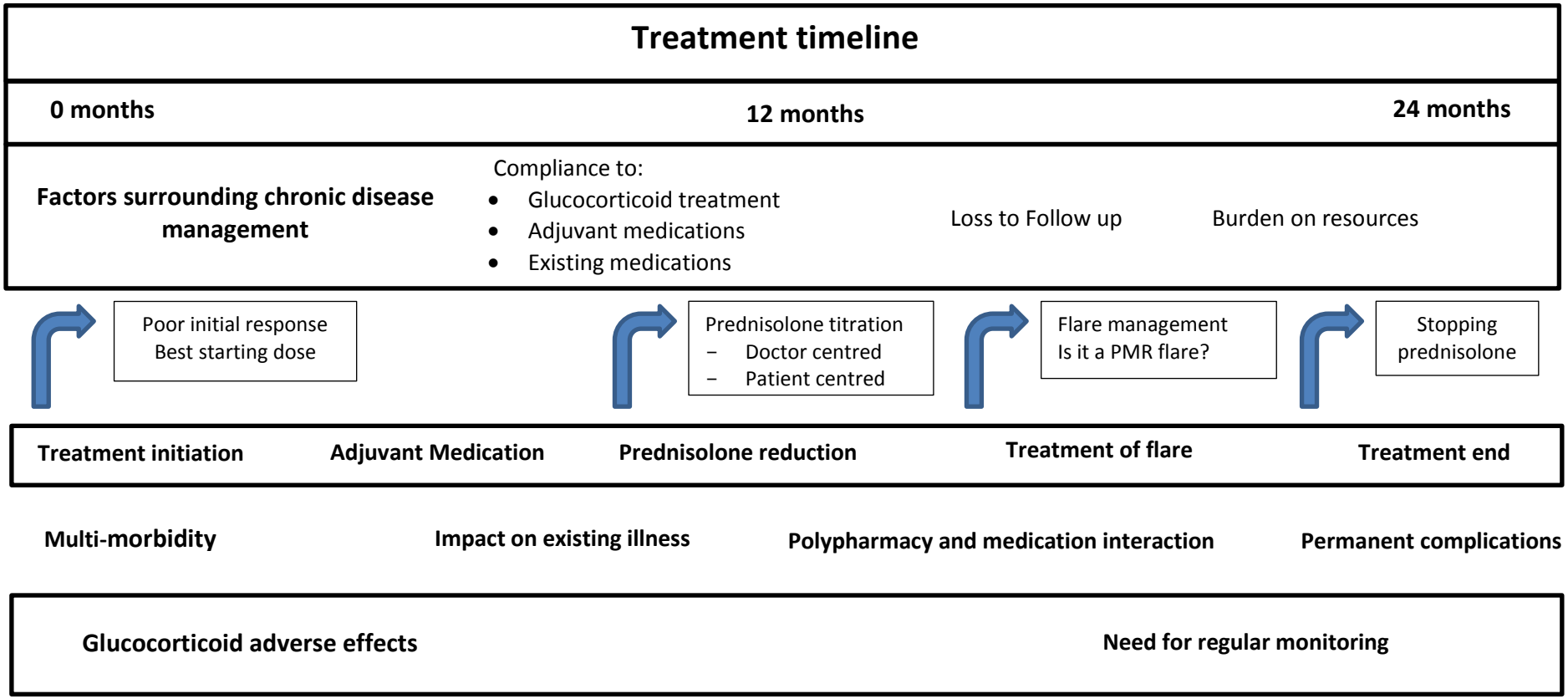
> *"diagnosis not always straightforward. Easy for patients to be lost to follow up if stable. May end up on steroids for years without proper monitoring, especially if change of surgery due going into nursing home for instance"*
>
> **Participant 814 (23, F, SP)**

Finally some participants expressed issues surrounding the lack of rapid access to specialist input and inconsistencies surrounding available guidelines.

> *"long term steroid complications require careful and frequent follow up, national and local guidelines and actual practice muddled with agreement, difficult access to secondary care, concern they mix up diagnosis timeline"*
>
> **Participant 3927 (18, F, SP)**

Figure 5.6 summarises the challenges described by participants in the questionnaire postal survey, including the points where treatments are added or changed during the treatment period.

Figure 5.6 Treatment timeline for PMR and management challenges during the treatment timeline

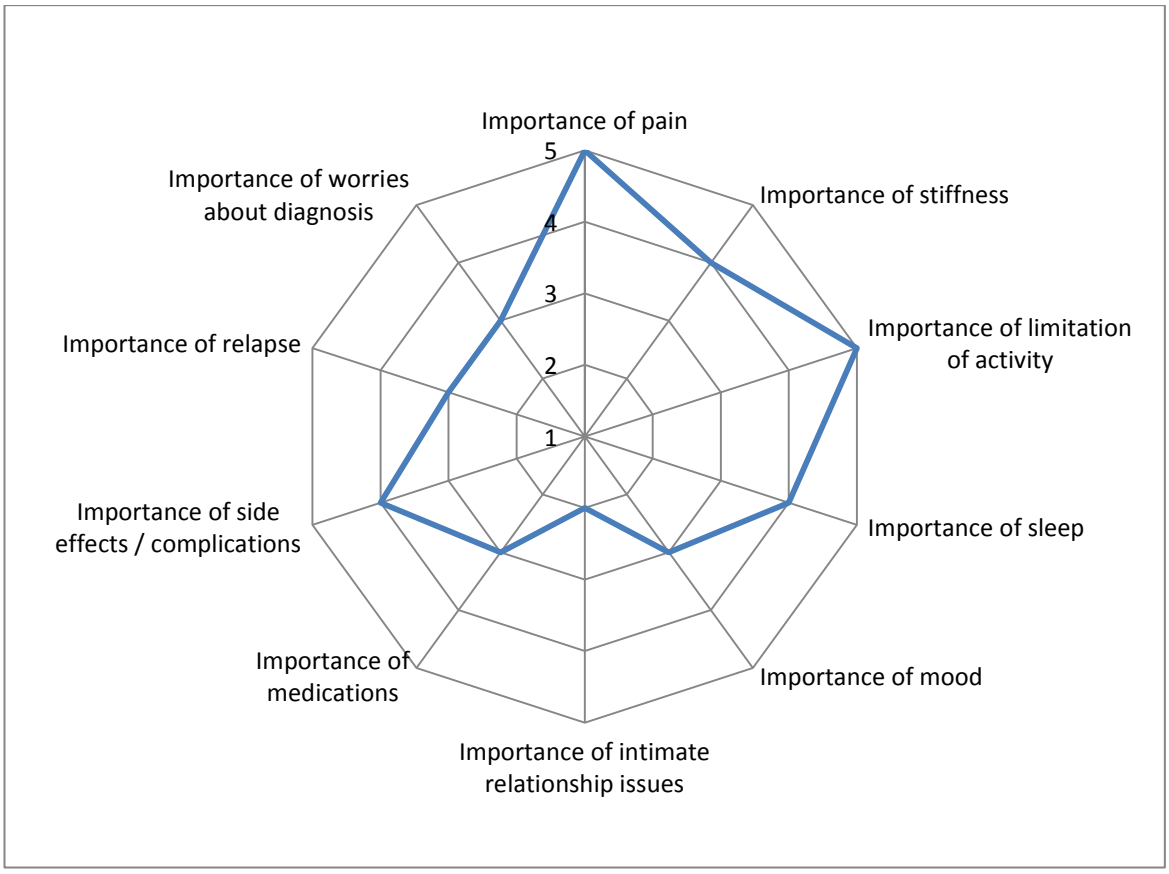


5.6 Perceived impact of PMR on patient's lives (Question 13)

The questionnaire also asked participants about how they perceived PMR impacted on their patients' lives. GPs were asked to rate the importance of various PMR features (5 being very important and 1 being least important) that may impact on well-being and function (Figure 5.7).

These results suggest that GPs perceive the greatest PMR related issues that patients have to be pain and limitation of activity, followed by sleep issues, stiffness and concerns surrounding side effects and complications of long term treatment.

Figure 5.7 Radar plot of median scores of perceived impact of PMR on patients



5.7 Discussion

This large cross-sectional survey is the first to explore the views of GPs towards the diagnosis, management and challenges that PMR poses in primary care settings. The results suggest that PMR is a very challenging disorder to convincingly diagnose and manage effectively in primary care.

The quote below summarises in a participants own words many of the issues identified from the results of the questionnaire survey in diagnosing and managing PMR in general practice.

> *"There are challenges to make the diagnosis with the resources and time GPs have i.e. 10 minute consultations, lack of immediate blood results, time and resources, patients require regular review, blood tests, specific advice, management of side effects of treatment can be sometimes difficult in primary care"*
>
> **Participant 2506 (4, F, P)**

5.7.1 Summary of findings

Issues regarding accurate diagnosis remain the predominant challenge associated with PMR for general practitioners. First, the wide range of differential diagnoses, sometimes vague presentation and atypical features can make identifying PMR patients very difficult. Added to this, patients in the typical PMR age-range often have multi-morbidity which can confuse the presenting picture and complicate treatment regimens. A PMR diagnosis will result in long-term treatment with glucocorticoids with its associated potential

adverse effects which can also impact on comorbidity. An accurate diagnosis is therefore imperative.

GPs responding to this cross sectional survey appear to be identifying patients with PMR using widely accepted clinical features, although there may be some over-reliance on response to treatment, both with respect to making or excluding a PMR diagnosis. Multi-morbidity and/or poly-pharmacy increases with age [Uijen and Van De Lisdonk 2008] and so is a particular issue for diagnosing PMR (given that PMR is rare under the age of 60), as it may impact on the clarity of PMR symptoms, which will contribute to the diagnostic challenge. Multi-morbidity and/or polypharmacy also therefore relates to the challenges of excluding mimicking disorders which may be responsible for symptoms. It is an area that is clearly causing concern amongst responding participants, but is especially important in light of evidence that suggests an excess in malignancy diagnosed in the first six months after being diagnosed with PMR may be attributed to misdiagnosis. [Muller et al 2013] A clear process of exclusion of alternative diagnoses and on-going surveillance represents an area where improvements in practice could be made. Analysis of the open response questions relating to this issue suggested that there was not a set standard of investigations participants were routinely performing and has been found in other research in this area. [Helliwell et al 2013] This could be a reflection of a lack of awareness of the current guidance and advised investigation set, or, that GPs are simply choosing not to follow guidance. A process of exclusion of mimicking disorders however is an important and essential aspect of diagnosis and represents and area where practice could be improved. This could be achieved through focused dissemination of the current guidance through educational initiatives and relevant literature for practising GPs.

Normal inflammatory markers have been shown to occur in up to a 22.5% of cases. [Ellis et al 1983] However diagnosis has to be carefully considered in cases where inflammatory markers are normal, and should prompt a referral for specialist review for possible alternative diagnoses. [Dasgupta et al 2010] Over half of responders indicated that they would initially offer a trial of treatment. This is a significant potential pitfall, given that the symptoms of some disorders including inflammatory arthritis, non-inflammatory musculoskeletal disease and some malignancies will temporarily improve with oral prednisolone reinforcing that a systematic exclusion of other causes for symptoms does not appear to be routine practice.

However, whilst guidelines are helpful and advocate the exclusion of all other potential causes for symptoms they do not often address issues surrounding multi-morbidity [Muth et al 2014] and the possibility that more than one condition may contribute to the presenting symptoms. Accounting for this is often dependent on clinician experience, which may be difficult to accrue with uncommon disorders like PMR. In the absence of a robust diagnostic protocol or gold standard diagnostic test, accurate diagnosis will still depend on the experience of the clinician in conjunction with vigilant follow-up and support from specialist services aided by accepted guidelines.

PMR management in terms of treatment with glucocorticoids remains a source of on-going concern for clinicians with regards to side effects, complications, appropriate dose reduction, monitoring, effects on co-morbidity and interactions with other concomitant medication. These are understandable given that in PMR patients, cumulative glucocorticoid dose is associated with fragility fracture (OR 1.4) and duration of treatment is associated with the development of osteoporosis (OR 1.02) and arterial hypertension

(OR 1.03). [Mazzantini et al 2012] Overall management of PMR in primary care appears to be broadly in-line with UK BSR/BHPR guidance however some responders felt that guidance was not clear on the initiating dose of prednisolone and is reflected in the finding that almost 40% of responders are initially treating PMR with inappropriately high doses of prednisolone. The BSR/BHPR UK guidance, however is clear on the initiating prednisolone dose (15mg of prednisolone which can be increased to 20mg if the clinical picture is convincing and a response to treatment is sub-optimal) and may suggest that guidance has not been disseminated yet to the wider GP population or GPs are simply not following the advised guidance. [Dasgupta et al 2010]

What is less clear in the guidance is the reduction of treatment from this initial dose. Whilst there is also an advised prednisolone reduction regimen, in practise, prednisolone reduction can be more variable and may depend on multiple factors which as yet have not been investigated. For example inter-current illness, co-morbidity, severity of disease, genetic predisposition, gender, age at onset and pre-morbid state may all affect the dose reduction regimen. Dose reduction therefore is a much more complicated process and not one that could necessarily follow a fixed timeline.

Appropriate bone prophylaxis is reported to be routinely offered by the majority of responders which contrasts with observed findings that suggests that prophylaxis is not routinely offered. [Helliwell et al 2013] However many factors may impact on whether it is finally prescribed or not, for example polypharmacy, interactions, adverse effects and patient choice, and may account for this discrepancy.

The final significant challenge that PMR poses surrounds the significant amount of resources that are needed for regular follow up and the associated specialist support that may be needed in certain cases. Ensuring appropriate follow up for patients and for patients to remember to arrange further assessment can add to the challenge of on-going monitoring and is an area where, if not carefully considered, loss to follow up could be an issue and may result in inappropriately prolonged treatment. Excessively long treatment could result in inappropriate exposure to risks of treatment which additionally, may not be identified if not followed up regularly.

5.7.2 Factors contributing to the challenges associated with PMR

Musculoskeletal disorders account for around one in seven consultations in general practice, [Jordan et al 2010] yet confidence in diagnosis and management of musculoskeletal disorders remains consistently low. [Goff et al 2014] This was thought to be related to the differences in case mix that GP trainees are exposed to with trainees seeing younger patients with more minor and or acute problems. [Eccles et al 1994] However, Goff (2014) showed that this was not the case specifically for musculoskeletal disorders but rather the lack of provision of specific musculoskeletal training in general, even at to undergraduate level. [Goff et al 2014]

A survey of GP trainees demonstrated that the rheumatology training was insufficient, that the training they did have depended on whether they had been posted on rheumatology placements, and online resources [personal correspondence with Louise Warburton 23/11/2015].

The age-adjusted incidence of PMR in the UK has been shown to be 8.4 per 10,000 patient years and a fulltime GP can expect to see 4 or 5 PMR patients per year [Jordan 2010], of which 1 or 2 patients may be newly presenting with PMR. [Smeeth et al 2006] In comparison, a full-time GP can expect to see approximately 45 patients with osteoarthritis, [Jordan 2010] and around 25 new cases of community acquired pneumonia per year. [Millet et al 2013] PMR therefore, is relatively rarely encountered in general practice despite being one of the most common inflammatory rheumatic disorders. For trainee general practitioners, exposure to PMR in a twelve month GP registrar training placement is likely to be extremely limited even if it does occur. Also, given the non-specific initial presenting features, it may not be immediately recognised when patients present early or atypically especially for practitioners with less experience of the condition.

The most recent BSR/BHPR PMR guidance advises on indications for referral for specialist review particularly in cases of atypical features and treatment dilemmas. [Dasgupta et al 2010] Rapid access for specialist PMR review remains an issue particularly if treatment has been initiated, as it can affect how a patient presents at their specialist review adding to diagnostic difficulty and challenge for the assessing specialist, especially when the appointment is weeks or even months after treatment has been started. [Quick and Kirwan 2012] Rapid access for specialist review for potential PMR patients presenting atypically would be an optimum solution for this, ideally with patients being seen prior to the initiation of treatment so that the clinical features are not affected

The PMR guidelines currently available represent a much needed baseline reference resource for clinicians. Previously, no unified guidance was available, however, no guideline can cover every aspect of an illness and this is a particular problem for PMR given the range of presenting features. Furthermore, the guidance does not consider the impact of multi-morbidity which is a significant problem in older patients. Finally, these guidelines were published in a rheumatology specialist journal and may therefore not be accessed by GPs, although the guidelines have been disseminated to primary care in a number of publications including the British Journal of General Practice [Helliwell et al 2012] and the Arthristis Research UK "Hands on" series, which is sent to all GPs in the country. [Mallen et al 2014] The following Section discusses some of the potential strengths and weakness of the survey findings.

5.7.3 Potential sources of biases

This section discusses potential sources of bias that may be relevant to this study including response bias, recall bias, social desirability bias and volunteer bias.

5.7.3.1 Response bias

The questionnaire response was 24.98%. This is comparable to similar musculoskeletal related GP surveys undertaken recently within the Research Institute (for example [Clarson et al 2013]), but is lower than mean response in published articles using survey methods. [Creavin et al 2011] Generally, response rates to surveys in primary care appear to be declining. [Creavin et al 2011] There may however, be specific reasons why the

response rate for this study is lower than expected. Although a single prize of champagne has been shown to be an effective incentive [Thomson et al 2004] this may have been insufficient to promote response for this study.

Workload can impact on decisions to participate in surveys. [Kaner et al 1998, McAvoy and Kaner 1996] GP workload has significantly increased over the past 5 years and may be a factor contributing to the overall reduction in research participation. Many GPs may simply have been too busy to participate, or the disruption to workload too great to complete a questionnaire. PMR is a relatively uncommon condition and may not have been a sufficiently interesting topic for many GP's. Equally some may not have known much about the subject and so lacked confidence in participating. A lack of interest in the subject is a well-recognised factor that can impact on decisions about taking part in surveys or not and would have impacted on survey response. [McAvoy and Kaner 1996] Study participants however, may have had a special interest in musculoskeletal medicine which could result in them having an increased awareness of the issues and challenges that are associated with this condition or they may be more likely to report clinical practice in line with best practice guidelines. Given the previously described results, demonstrating marked deviation from some areas of current clinical guidelines it is unlikely that the results presented in this chapter are heavily skewed to those with an interest in this area.

Low response creates concern due to the potential for bias and the lack of generalisability. However this is only the case if the responding participants are significantly different from the population sampled. Despite the limited data that is

available on non-responders it is possible to make some observations. Responders to this survey appear to work in slightly larger practices with a greater number of partners than non-responders. However, responder demographics relating mean age, gender, and GP role were comparable to national demographics. [GP Data. www.hscic.gov.uk/]

5.7.3.2 Recall Bias

Recall bias defined as a "*Systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences"* [Dictionary of epidemiology 2014]. Recall bias has been shown to increase with rare disorders. [Sackett 1979] Recall of events and critical details is a complex process and can significantly affect responses to survey questions. Recall declines with increased time lapse since the exposure or experience, emotional or personal experiences associated with an event, and the number of previous exposures. [Bradburn et al 1987] Given the infrequency with which GPs encounter PMR, recall issues may have been an issue for some participants impacting as a result on the accuracy of the data provided.

5.7.3.3 Social desirability bias

Phillips defined social desirability bias as *"tendency of people to deny socially undesirable traits or qualities and to admit to socially desirable ones".* [Phillips and Clancy 1972] This can be a particular issue with questionnaire surveys as they rely on responders to accurately respond to questions in an honest and truthful way to reflect their opinions, experiences and knowledge. Social desirability bias tends to impact more on studies

relating to sensitive topics. [Gregson et al 2002] Whilst this survey did not ask sensitive questions, participants may equally not want their lack of knowledge to be known irrespective of how anonymised the study is. Questionnaire surveys cannot control or prevent participants from reviewing guidance or reporting best practice. Some participants to the PMR questionnaire survey may well have revised current guidelines whilst completing the questionnaire or may not have answered in a way that reflected their true practice. However, given the wide range of responses this is unlikely to have had a major impact on this study.

5.7.3.4 Volunteer Bias

Heiman (2002) suggested that volunteer bias is a form of bias that arises from the fact that a particular sample of participants will comprise of those are actually willing to participate and those who find the topic interesting. [Heiman 2002] Volunteers that participate have been shown to be different from non-volunteers in that they can be more educated, more intelligent, desire a need for approval and are more social. [Rosenthal and Rosnow 1975] This form of bias relates closely to the concept that responding to surveys is closely related to the level of interest that the participant has in the survey and needs to be acknowledged.

5.7.4 Strengths and weaknesses

5.7.4.1 Strengths

This is the first large scale national survey of general practitioners focusing on PMR diagnosis and management in primary care. This is an area where evidence is lacking. This large data-set provides a unique insight into PMR diagnosis and management in primary care from the GP perspective and thus adds to our knowledge of PMR and identifies targets that could help to improve care for patients. The survey was conducted using rigorous clinical trials unit (CTU) approved protocols, monitoring and quality checks to ensure a high quality data set is generated. In conducting this survey, standard operating procedures (SOPs) relating to survey management were used. This strives to ensure governance, quality and research excellence by including data entry checking processes and quality review processes of all paperwork by all members of the study team and lay advisors. The survey was developed using current guidance, and identified issues from previous primary care research [Helliwell et al 2013], as well as including input from practising rheumatologists and general practitioners. It was also piloted amongst a number of practising GPs and amended based on their recommendations. My involvement in this study and the recognition of this work has resulted in me contributing to the OMERACT (Outcome Measures in Rheumatology And Clinical Trials) PMR special interest group (as an OMERACT fellow) to develop a standard outcome measure set for PMR research. This work was also endorsed by the national PMR charity, PMRGCAUK who recognise this as an area of importance.

5.7.4.2 Weaknesses

Whilst there are limitations and biases that will apply to most questionnaire surveys and relate to survey methodology in general [Choi and Pak 2005], the main weakness of this survey relates to the suboptimal response and therefore the potential lack of generalisability of the data and the conclusions that can be made from it.

The questionnaire used in this study was designed specifically to investigate the primary care diagnosis and management of PMR and did not use predetermined and validated items or instruments. However, the questionnaire was developed using existing literature to support maximising response rates and was piloted amongst general practitioners and rheumatologists to assess usability and quality and to improve face validity.

5.8 Conclusions

This is the largest study to date investigating the management of PMR and GCA in general practice. Although issues surrounding response are evident, the findings highlight several issues that could contribute to improving care for patients with PMR including improvements in GP training, accessibility of appropriate and relevant guidance and access to specialist support if needed.

With a wide differential diagnosis and in the absence of robust diagnostic criteria or gold standard diagnostic tests, PMR remains a very challenging illness to diagnose. Clinical features, laboratory findings, previous experience, trials of treatment and vigilance to

ensure that there are no other causes for symptoms, all have to be drawn upon, for clinicians to diagnose PMR in primary care. This needs to be in conjunction with careful, on-going follow up to ensure that no other mimicking disorder becomes apparent.

Response to treatment with low to medium dose glucocorticoids has long been suggested a typical feature of PMR [Dasgupta et al 2010] and is a highly rated feature of PMR amongst general practitioners (see Figure 5.2). Over-reliance on this feature is however, a significant potential pitfall, especially as recent research findings question the diagnostic usefulness of this approach [Dasgupta et al 2012] and it is known that significant mimicking disorders, for example cancer, [Muller et al 2013] may be missed. Also, what constitutes an adequate treatment response? Guidance suggests that an adequate response is a patient reported global improvement of seventy percent or more but do GPs use such guidance when reviewing patients? [Dasgupta et al 2010] Perhaps, in order to improve diagnostic accuracy when considering response to treatment, a more formal approach to assess response or alternative approaches to initial treatment like a "treatment sandwich", where patients with PMR are treated for a period of time with glucocorticoids but then treatment is withdrawn and then restarted after a short period of time. [Quick and Kirwan 2012] Initial treatment dosing remains a controversial area in PMR and is an area where further research is needed.

Vigilant follow-up over time is key to ensuring a correct diagnosis and to screen and manage any associated treatment adverse effects (such as diabetes) or associations (for example GCA). A formal protocol or template driven review, as is undertaken for other disorders in primary care (for example epilepsy and asthma) may improve diligence in reviews given its rarity and so help to improve outcomes for patients. Issues still remain

and so the final objective of this thesis was to undertake a semi-structured telephone interview study of GPs to explore some of these issues and challenges in much greater depth. The methods and results of this study will be presented in the following chapter.

Chapter 6. A qualitative study investigating the diagnostic and management challenges of PMR in primary care

> *"It wrecks lives doesn't it? You get people that are, kind of, you know, really active, and then all of a sudden they've got this awful thing. And then they get the treatment for it that, you know, improves them"* **GP 22 (15, M, P)**

Key: [time qualified as a GP (years), gender (male/Female), seniority/role (S:salaried, L:locum, P:partner, SP: senior partner)]

6.1 Introduction

This chapter presents the qualitative interview study conducted as part of this PhD, allowing a more in-depth understanding of the data collected and presented in chapter 5. The first section of the chapter introduces and justifies the qualitative methods utilised, including recruitment and analysis. The second section presents the findings and conclusions of the in-depth GP interviews.

6.1.1 How a qualitative study fits in to this multi-methods thesis

Qualitative research methods seek to provide a more complete understanding of the research problem and are ideal for investigating in depth the complexity of a subject. [Howitt and Cramer 2008] A qualitative study may often be undertaken to inform a much

larger quantitative study so that appropriate areas of focus are identified and not missed. Qualitative studies are often also used to validate quantitative research findings and results.

The key characteristic however for this aspect of the PhD, is the depth and richness of data that can be obtained using qualitative methods in health research. This is particularly important for under researched disorders such as PMR where clinical presentation and management can be highly variable.

Qualitative research methods were therefore chosen to explore the current practice, challenges and barriers to effective care encountered by general practitioners managing patients with PMR in the community. The data from these interviews will help to build on the results and further explore some of the issues identified from the cross sectional survey described in Chapter 5. This approach will complement the results of the cross-sectional survey in several ways. These include:

- Providing a more experiential and detailed source of data that will allow a thorough exploration of key issues identified in the survey
- Allowing the opportunity to discuss potential solutions to help overcome any barriers identified
- Identifying new areas for future research or investigation

6.2 Methods

The following section describes and justifies the methods used in conducting the qualitative study that forms part of this thesis.

6.2.1 Interviews

"Interviews facilitate the collection of detailed personal data that provides a high degree of response quality and the opportunity for probing deeply into issues"

[Block and Erskine 2012 p429]

Interviews remain the predominant method for data collection in qualitative studies in health care settings and can be semi-structured (incorporating open ended questions that focus and direct the participant to the area of interest) or in-depth (where possibly only one or two topics are discussed in thorough detail where the interviewer's role is to help probe and clarify information as it emerges). [Pope and Mays 2000]

The cross sectional study described in chapters 4 and 5 provided a large amount of data that identified numerous challenges and areas of potential focus for in-depth study. Therefore, this interview study aimed to explore in more depth, issues and challenges relating to PMR that were identified from the survey data. Formal in-depth interviews would not allow the exploration of the range of issues that have been identified and therefore a semi-structured interview process was chosen to allow exploration of specific challenges guided by the interviewer, whilst allowing sufficient depth of questioning to thoroughly explore the related issues.

6.2.2 Data Collection

In qualitative studies, data can be collected in numerous ways from the analysis of video and audio consultation data, to text analysis from a range of different types of media. Interviews with participants are a commonly employed method of data generation and were used for this study.

Semi-structured telephone interviews with clinically active general practitioners were undertaken. Face to face interviews are often viewed as the best way to interview participants, [Novick 2008] as they provide additional visual cues that enhance the contextual quality of the data. Telephone interviews have certain advantages over face to face interviews, depending on the study and the type of data that is being sought. These are summarised in Table 6.1.

Table 6.1 Summary of advantages and disadvantages of telephone interviews

Advantages	**Disadvantages**
Cost effectiveness	Lack of rapport building
Time efficient	Loss of visual and non-verbal cues
Increased access to a widely dispersed geographical or inaccessible population	Unable to use visual aids
Relative anonymity	Potentially poorer quality data.
Safety (both for researcher and participant)	Potentially lower response rate

Table developed from [Block and Erskine 2012]

One of the major limitations surrounding telephone interviews concerns the quality and richness of data resulting from the loss of visual cues and non-verbal and contextual data. It is also argued that rapport building with the participant and the ability of the interviewer to probe and elaborate on themes developing through the interview is not as effective with telephone interviews. However, these findings have not been formally

demonstrated and may not be relevant when researching certain populations, provided appropriate preparations have been made. [Novick 2008] This includes the provision of prior information to the participants and the development of appropriate topic guides which include specific questions to be asked in the interview. [Block and Erskine 2012, Sturges and Hanrahan 2004, Stephens 2007]

Despite the potential drawbacks of telephone interviews, they were chosen for data collection for the study for several reasons. Firstly, telephone interviews have the benefit of reaching a broad and geographically diverse cohort of participants, important as this was a UK wide study. Telephone interviews provide a convenient (for both interviewer and interviewee) and cost efficient opportunity to interview a broad range of participants. This convenience has the potential to improve participation of this study population given that GPs are often busy with limited available time to be interviewed. Telephone interviews also provide a certain amount of anonymity to the participant which is important to ensure that participants do not feel judged or tested by the interviewer, particularly important when the interviewer is from the same professional group as the interviewee, as in this case.

6.2.3 Participant Recruitment

6.2.3.1 Study population

General practitioners are the first line of contact for most patients developing symptoms of PMR and will often be involved in the on-going management and monitoring of the diseases. [Dasgupta et al 2010] Hence interviews with GPs were undertaken to provide a

more personal experience of PMR from a GP's perspective. This enabled the exploration of some previously unknown perspectives on the diagnosis, management and monitoring of PMR in a primary care setting.

6.2.3.2 Sampling Methodology

The postal survey (described in Chapters 4 and 5) provided a sampling frame for identifying participants. GPs responding to the postal survey were given the opportunity to consent to further contact from the research group. A total of 659 participants agreed to further contact. Potential participants were then purposively sampled from this database and sent a study pack inviting them to take part in the qualitative study.

6.2.3.3 Purposive Sampling

Silverman describes purposive sampling as:

"a method that allows us to choose a case because it illustrates some feature or process in which we are interested." [Silverman 2010 p148]

This sampling method, often used in qualitative research, does not aim to identify participants in order to produce data that is widely generalisable. Instead the method identifies participants that will potentially contribute the most information and so for this study, participants were specifically identified in order to generate data rich in variation of views and experience. Additionally, recruiting participants from different geographical

areas is essential to investigate regional variations in clinical practice and pathways of care.

To reflect as broad a range of practitioner experience as possible we purposively identified potential participants based on years of experience (more or less than 11 years (the median years of experience reported in the survey) of clinical experience as a GP), gender and seniority (locum, partner, salaried). 29 locum doctors responding to the original survey agreed to be contacted again. This group, in view of the transient nature of the work were expected to be a hard to reach group and so all of the identified locums were sent a study pack to take part in the study.

6.2.3.4 Sample Size

Interviews were conducted until data saturation is achieved. Data saturation is described by Strauss (1998) as the point when no new information, concepts or ideas are being found from the data. [Strauss 1998]

Estimating when saturation will occur remains controversial and difficult to predict and will vary depending on the study design, topic being researched, the participants and methods of interview. [Bazely 2014] Estimations for the number of participants required are often needed however in order to plan for study costs, project administration and work time allocation. Guest demonstrated using qualitative interview data from their study exploring social desirability bias, that 12 interviews was sufficient to achieve data saturation [Guest et al 2006] whilst other studies advise data saturation for the type of

study described in this thesis to occur after approximately 20 to 30 interviews. [Welsh et al 2012, Ryan and Bernard2000]

While the number of interviews required can be estimated, often the number of participants that need to be approached to achieve the required number of interviews is greater. Experience at the Keele University Research Institute of Primary Care and Health Sciences, based on previous studies purposively recruiting GPs for qualitative telephone interviews, found that approximately 130 general practitioners would need to be approached in order to recruit 30 participants for interview [e.g. Welsh et al 2012].

Figure 6.1 illustrates the process undertaken for recruiting GPs into the qualitative study. After purposively identifying potential participants to take part, study packs were sent by post after confirming that identified participants had agreed to further contact.

Study packs contained a covering letter of introduction, participant information leaflet and participant consent form. These documents can be reviewed in Appendix 5 and were designed using templates obtained from the Keele University Institute of Primary Care and Health Sciences Standard Operating Procedure 7 [SOP 7 - Document Design and Development].

Participants responding to the study pack were logged on a mailing database developed for the study. Those who provided consent to take part in an interview were then contacted by their preferred method (telephone or email) to formally arrange a convenient time for telephone interview.

6.2.3.5 Reimbursement of participants

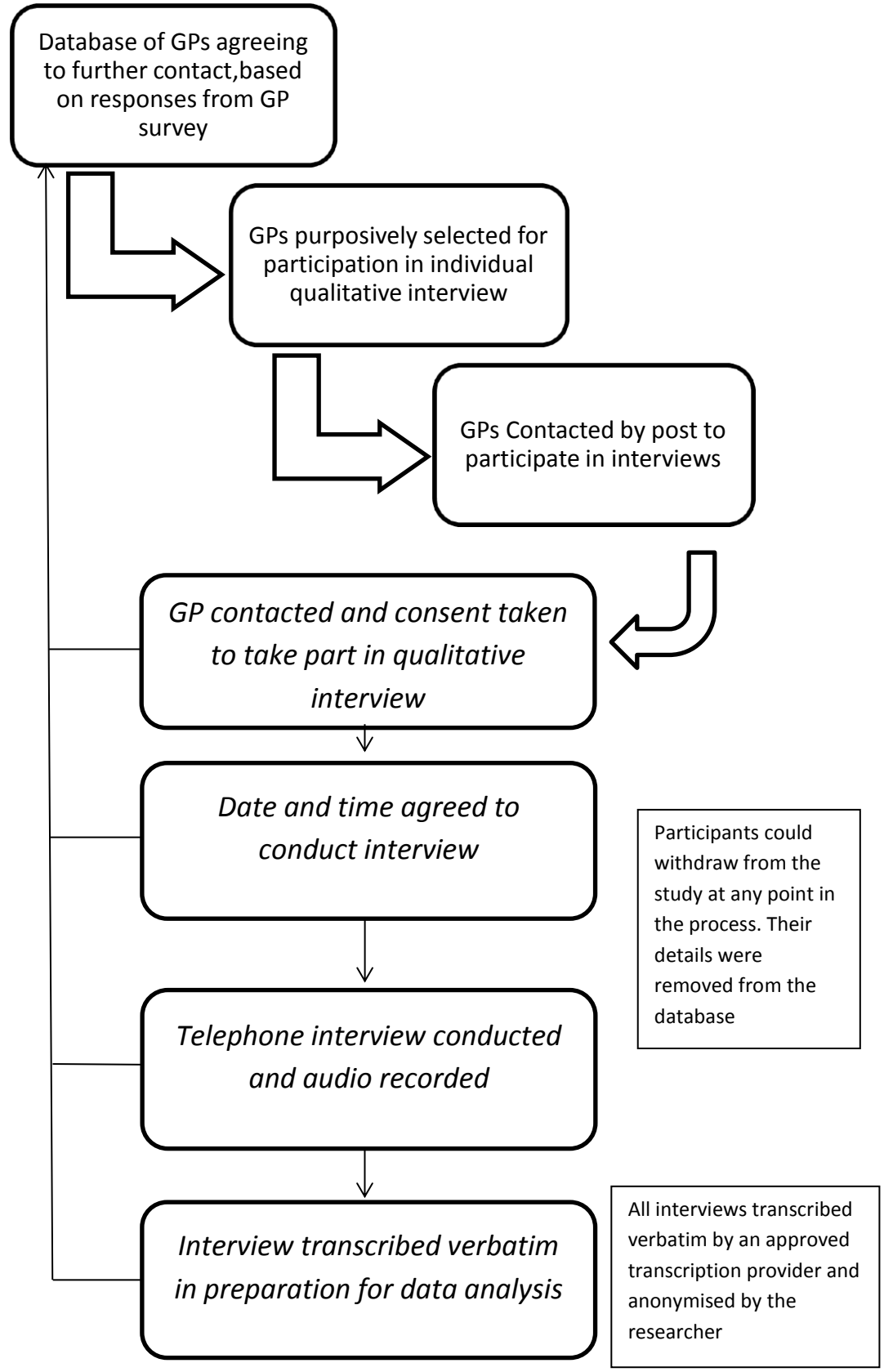
A reimbursement of £50 was offered to participants for taking part in the study. The amount was calculated based on typical hourly payment rates for locum GPs, and was provided as an acknowledgement of the time that the GP had given up to take part, rather than as an incentive to participate.

6.2.4 Topic guide development

A topic guide was developed to maintain interview structure, to ensure essential administrative procedures were undertaken (including checking consent, discussing reimbursement, confirming that the interviews would be recorded and transcribed) and to ensure that all relevant topics surrounding PMR and GCA were discussed. Topics to be discussed were informed by areas of interest from the findings of the quantitative cross sectional survey and relevant areas of interest from the wider PMR literature. The topic guide was reviewed and refined with feedback from GPs, rheumatologists and qualitative researchers. This process is summarised in Appendix 5.

As transcripts were reviewed, and as experience was gained from the interviews undertaken, the topic guide was modified to focus on themes that started to emerge from the interviews. The final topic guide can be seen in Appendix 6.

Figure 6.1 Flow Chart illustrating GP recruitment



6.2.5 Interviewer training

TH undertook specific qualitative interview training, attending the Oxford University 'Introduction to qualitative interviews' course. A pilot interview was also undertaken with an independent GP volunteer. The pilot interview was reviewed by a senior qualitative research supervisor (JR- Dr Jane Richardson) with expertise in qualitative interviewing and specific feedback was given. This focused on conducting the interview to allow the participant to tell their story, to develop techniques on how to encourage the interviewee to really explore the topic being discussed and how to interview GP colleagues objectively given the relative expertise that the interviewer has.

6.2.6 Practical consideration in performing telephone interviews

The interviews were conducted by TH at times convenient to the participants. Owing to the busy schedules and limited time that GPs have to undertake such interviews, the maximum amount of flexibility was offered resulting in interviews being conducted throughout the day and sometimes late in the evening.

Interviews were digitally recorded and the resulting interviews were uploaded to a secure, password protected folder. Interviews were then transcribed verbatim by an approved transcription company (The Transcription Company, http://thetranscription.co.uk/) used by Keele University Research Institute of Primary Care and Health Sciences. Resulting transcripts were then screened to remove any identifying information prior to analysis.

Analysis of the transcripts was managed by using NVivo (NVivo10) [NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 10, 2012]-a qualitative data analysis software package analysed using a thematic analysis, described in Chapter 4.

6.2.7 Methods of qualitative data analysis

6.2.7.1 Thematic and framework analysis

Thematic analysis is one of the most common forms of analysis used in qualitative studies. Braun and Clarke argue that it is an analysis in its own right [Braun and Clarke 2006], but thematic analysis does have its critics, not so much related to the method but more related to a lack of, or superficial methodological detail reporting and theory development [Bazely 2014]. Braun described six phases in thematic analysis. These are illustrated and summarised in Table 6.2 and this framework was used to analyse the transcribed interviews.

TH undertook thematic analysis training through the Oxford University "analysing qualitative interview course". Additionally, as quality control, an inter-rater exercise was undertaken in which three other researchers (SM, SH, JR) were asked to independently analyse and identify general themes relating to an interview to compare with findings by TH.

Table 6.2 The Six phases of thematic analysis

Phase	Description
Phase 1: Familiarisation	This may occur during the process of transcription or initial reading of transcribed interviews
Phase 2: Generating initial codes	Systematic coding of interesting features and gathering all relevant data to develop any potential themes
Phase 3: Searching for themes among codes	Grouping codes into potential themes Developing a thematic map
Phase 4: Reviewing themes	Confirming that identified themes relate to coded extracts and the relevant codes across the data set
Phase 5: Defining and naming themes	Formalise the specific themes and how they relate to the overall story
Phase 6: Producing the report	Final check on the overall themes relating to the overall story and related literature

[Braun and Clarke 2006]

Pope also discusses a “framework” approach to analysis which is a development of thematic analysis which was developed specifically for applied or policy relevant qualitative research where the objectives are known prior to the study being conducted, relative to the needs of the researching body (e.g. a health authority). Pope describes 5 stages of data analysis including:

1) Familiarisation,
2) Identifying a thematic framework,
3) Indexing,
4) Charting
5) Mapping and interpretation.

This method is based on both the findings from the original data obtained from participants and the aims and objectives already set for the study [Pope and Mays 2000]. A thematic analysis was therefore used but was influenced by some aspects of framework analysis given the thematic analysis was influenced by the survey findings.

6.2.7.2 The physical process of data analysis

The analysis process began as early as undertaking the pilot interview. Although not a formal participant whose interview would be used for analysis it did start the process of understanding where and what the potential themes surrounding PMR and GCA might be. Feedback from a senior qualitative researcher (JR) helped me to understand how best to explore issues better for future interviews without making the interviewer feel judged by phrasing questions based on what other GPs had said or the findings of the survey. Analysis began after transcribing the two initial interviews. Although time consuming and not being expert in transcription techniques this process was extremely useful as it allowed a thorough familiarisation with the data which enabled me to identify and reflect on initial codes, themes and subthemes. For all other transcripts that were transcribed professionally, an initial read through and anonymization or removal of identifiable data was undertaken. Whilst this had a pragmatic justification it also allowed familiarisation with the data to reflect on possible codes and to review the field notes to see if there was a particular focus or specific agenda for the participant being interviewed. Interview eight was chosen to be reviewed and coded by my supervisors (JR, SM, SH). This interview was chosen as it contained broad variety of issues, and was undertaken after gaining some

experience in interviewing and analysis whilst not being too far through the analysis process so any issues could be identified and addressed for future transcripts.

Thorough analysis of each transcript was then undertaken by identifying initial codes to develop into sub themes and themes. Coding was undertaken using NVivo 10 which is a qualitative data analysis software package. Whilst I encountered many benefits and some frustrations in using this software, it did make the task of analysis with subsequent code generation much easier than analysing transcripts using hard copies of the interviews. In particular, coding and the development of sub-themes and themes was straightforward through the development of nodes (a method of categorising in NVivo) that could be accessed to add relevant text for each transcript. Also, text searching and cross referencing was straight forward and rapid to perform which was of particular help when emerging themes and subthemes were being developed. These functions allowed comparison of data from the interviews with particular codes or themes to see if similarities existed. Finally, node related data was another helpful feature of this software. Whilst qualitative methods do not necessarily call for frequencies to assign relative importance, knowing how often a code is used can give an idea of the impact and importance of that code.

The predominant challenge that I encountered during the analysis phase was the preconceived ideas that I had, given that I am a GP as well as having research experience in PMR and the findings from the PMR cross-sectional survey that was informing the interview topic guide.

Qualitative analysis requires a considerable amount of interpretation and so I had to be mindful and reflective of my preconceptions and be vigilant and sensitive to identifying other issues that may emerge. In some ways, being aware of the issues could be an advantage for this study as it allowed me to be able to recognise early potential areas of enquiry that had not been identified in the usual literature or from the survey.

6.3 Results of qualitative interview study

The following section describes the baseline demographics of the interviewed sample and reports the findings from the qualitative interview study of GPs.

6.3.1 Participant Recruitment

659 participants who had agreed to further contact regarding future research were identified from the cross-sectional postal survey and used for the sampling frame to recruit GPs for the qualitative interview study. Study packs were mailed to purposively identified potential participants, initially in batches of 30. The number of packs mailed was subsequently increased to batches of 60 after an initially poor response from GPs. A total of 327 study packs were mailed to GPs over a period of nine months. Table 6.3 illustrates the breakdown of who was sent study packs relative to our purposive sampling framework.

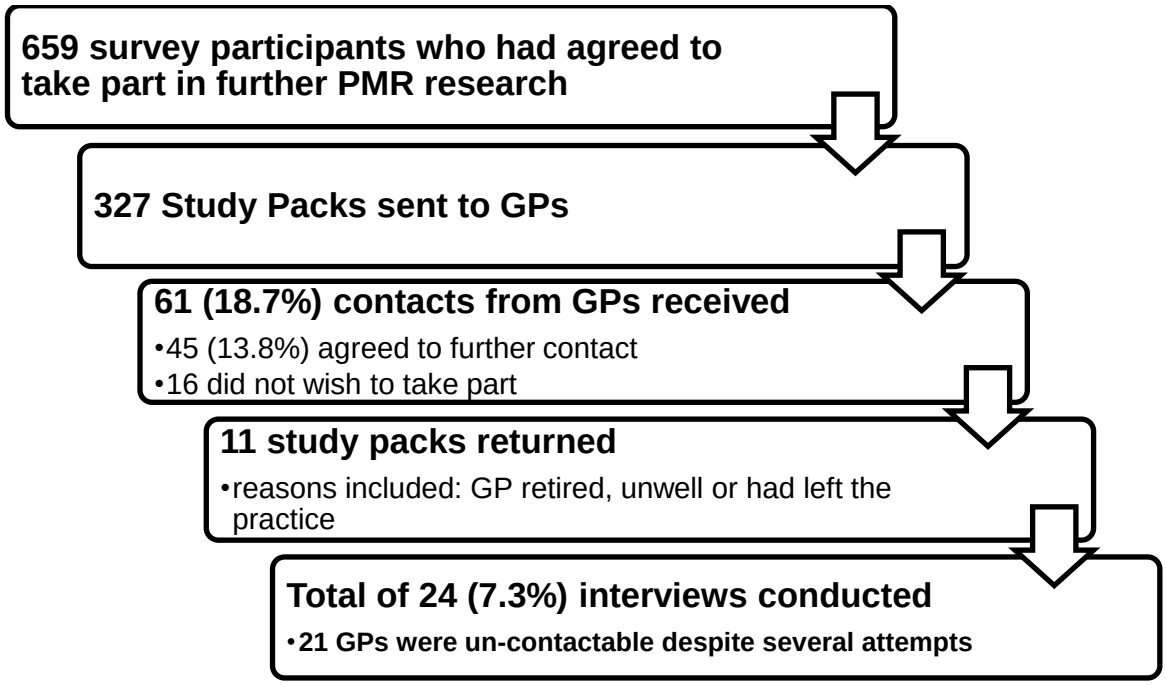
Table 6.3 Purposive Sampling Breakdown of categories

Gender	Experience	Seniority	n (%)
Female	Less than 11 years	Partner	98 (44%)
Male	Less than 11 years	Partner	124 (56%)
Female	Less than 11 years	Salaried	64 (70%)
Male	Less than 11 years	Salaried	27(30%)
Female	More than 11 years	Partner	105 (43%)
Male	More than 11 years	Partner	139 (47%)
Female	More than 11 years	Salaried	32 (71%)
Male	More than 11 years	Salaried	13 (29%)
Locums			29
Total female			299
Total male			303

n= number in this category

61 (18.7%) contacts were received from GPs. 45 of these agreed to be contacted again and participate in the interview study, resulting in 24 (7.3% of total mailed study packs) completing interviews. The remaining GPs did not respond to further contact regarding the interview study, despite repeated attempts using their preferred method (e.g. telephone, email). This process is summarised in Figure 6.2.

Figure 6.2 GP recruitment process for the telephone interview study



6.3.2 Characteristics of Interview Participants

The characteristics of participants who completed a telephone interview are illustrated in Table 6.4. Unfortunately no locum participants responded to our survey packs, which is perhaps not surprising, as this group was expected to be hard to reach (e.g. moving to work in a different practice or geographical area), especially given the time interval between the initial survey and mail out for the qualitative study.

Table 6.4 Characteristics of GPs participating in the PMR qualitative interview study

GP Identification	Gender	Years Qualified as a GP	Seniority	Region
GP1	F	13	Partner	Eastern
GP2	F	29	Partner	South West
GP3	M	9	Partner	London
GP4	M	6	Partner	South West
GP5	F	15	Partner	South East
GP6	F	20	Partner	South west
GP7	M	10	Partner	Scotland
GP8	F	10	Salaried	London
GP9	M	19	Partner	Wales
GP10	F	12	Salaried	Yorkshire
GP11	F	10	Partner	Eastern
GP12	F	15	Salaried	Yorkshire
GP13	F	5	Salaried	Yorkshire
GP14	F	9	Partner	Derbyshire
GP15	F	25	Partner	Cumbria
GP16	M	17	Partner	Midlands
GP17	F	11	Partner	North Scotland
GP18	M	22	Salaried	Midlands
GP19	F	8	Salaried	South East
GP20	M	17	Partner	Midlands
GP21	F	7	Salaried	Surrey
GP22	M	15	Partner	South East
GP23	F	13	Salaried	Eastern
GP23	F	12	Salaried	Eastern
GP24	F	12	Salaried	Midlands

F: Female
M: Male

There was a good geographical spread of participants with a range of overall experience in terms of years qualified as a GP. Figure 6.3 depicts the areas where the GP participants were located. Verbatim quotes are presented in the same manner as in Chapter 5, illustrating their experience (duration of qualification as a GP), gender and seniority/role and are presented in the following format using the following key.

Key: [time qualified as a GP (years), gender (male/Female), seniority/role (S:salaried, L:locum, P:partner, SP: senior partner)]

Figure 6.3 Geographical locations of GP participants.

6.3.3 Results of thematic analysis of GP interviews

The two main areas of interest surrounding PMR that were identified from the GP cross sectional survey concerned diagnosis and treatment. Information concerning the themes that was identified from the transcript data will be presented under these two broad headings, although they should not be viewed as mutually exclusive. Initial treatment plays an integral part in the diagnostic process for PMR, as there is considerable inter-linking between these two areas. The connection between making the diagnosis and then testing the likelihood of the diagnosis (by assessing response to glucocorticoid treatment) coupled with knowing the impact of long term treatment will have for the patient, has considerable influences on how clinicians make their initial diagnosis.

> *"Well they always get a response because everything responds to steroids and so it's much more the problem the other way round, that you're not very sure whether they've had a response because they're generally achy and this magic makes everything better. So I've never encountered somebody who didn't feel better on steroids and sometimes I'm not really convinced that it's the magic cure that they think it is. And so I mean I must say I would always err on the side of trying to not use steroids as my, you know in the end I think the patients are usually quite happy to be on steroids until they realise what a dreadful sentence it is really"*
>
> **GP17 (11, F, P)**

6.3.3.1 Diagnosis

> *"I mean, nobody ever comes in saying that they think they've got PMR……except those that have had it before. Or those that have got, you know, a close relative."*
>
> **GP 22 (15, M P)**

Relating to diagnosis there were two identified overarching themes. The first, "developing the diagnosis" relates to how patients present and how a GP may identify and diagnose patients with PMR. Response to initial treatment is specifically discussed in this section as a common feature of PMR is the rapid and significant response to glucocorticoids. The second, theme, "contributors to diagnostic uncertainty" relates to a range of factors that affect diagnostic confidence. Again these two themes are inherently connected.

6.3.3.2 Developing the diagnosis

The following section describes the sub-themes that contribute to the theme relating to developing a diagnosis.

Awareness of PMR

This sub theme is relevant to both patients and clinicians. For many patients some of the symptoms of PMR may almost be an expected part of aging and so patients may not (initially) recognise that there is anything wrong and subsequently may not seek medical help. This may especially be the case for patients with a gradual onset of symptoms or those with milder disease

> *"I think a lot of the time it's much older people, and they've just, kind of, gone, 'Well, it's part of getting old. I'm a lot achier than I was this time last year and they don't realise that it's necessarily something we could perhaps help with."*
>
> **GP23 (13, F, S)**

PMR may not be at the forefront of GPs' minds for several reasons, as it is infrequently encountered in general practice. [Smeeth et al 2006, Jordan et al 2010]

> *"Well, I suppose, quite unusual, maybe the GPs aren't aware of it. Or, you know, it's not something that you see all the time…."*
>
> **GP8 (10, F, S)**

Clinical Features

Respondents in general used the 'classical textbook' features to try and identify patients who may have PMR but were acutely aware that it can sometimes present clinically in an atypical way.

> *"I think the majority of the time people do come in with what's described as the classic symptoms; talking about pain mainly around shoulders and hips. I think those are the classic things that would make me think of it fairly quickly. I suppose there are then people who come in with much more generalised non-specific aches and pains, and it can then take a little bit longer for PMR to come to the forefront of your mind when seeing them. I suppose systemic features as well; so if people have aches and pains but it also comes on fairly rapidly, with them initially often feeling generally unwell with it as well, that would make me think about it"*
>
> **GP13 (5, F, S)**

GPs often however, related the symptoms of PMR to the functional impact on patients, as patients often recognise that there is a problem because of certain tasks that they have problems with.

> *"Typically, when they're complaining of shoulder pain, and they say, 'I've had real trouble washing my hair or brushing my hair.' And there's difficulty with getting up out of the chair because of the leg pain, you know, the, sort of, ones that give you the high index of suspicion."*
>
> **GP23 (12, F, S)**

Investigations

Guidance suggests a range of blood tests and investigations to undertake when diagnosing PMR to confirm the diagnosis and exclude common differential diagnoses. [Dasgupta et al 2010] All participants reported undertaking blood tests to measure an inflammatory response. Several factors directed other investigations that would be requested depending on the degree of diagnostic certainty, presenting features or associated features of concern.

> *"I mean obviously the cardinal things I'm looking for are raised inflammatory markers so CRP and the ESR would be the two that I would be sort of looking at. However I would be doing a full blood count because it's not uncommon that I'd find a mild anaemia, a chronic disease. I'd do renal function because I'm going to be sticking them on drugs potentially, similarly liver function tests, I want a baseline glucose and potentially an HbA1c if I think that's going to be abnormal. I may want to do a CK [creatinine kinase] because there's often sort of myalgia. If there's been any weight loss already or any other sort of slightly sort of more sort of red flag symptoms I'd be considering things like an auto immune profile or myeloma screen, tend to do a chest X-ray at baseline when I'm starting with the steroids but earlier than that if there's any other systemic features, yeah so I think that's probably about it."*
>
> **GP6 (20, F, S)**

Factors causing diagnostic uncertainty

A recurrent finding indicated by GPs was that patients can present atypically, especially older patients. Normal inflammatory markers with typical clinical features of PMR, was found to be a particular area that can cause diagnostic dilemmas.

> *"I had a colleague here when we were considering a diagnosis of somebody and we looked it all up in the book again and it said, basically you know you have to have X out of Y symptoms don't you there's like a list. And you can have a normal CRP it doesn't preclude it and so I don't know it's just - words fail one really"*
>
> **GP17 (11, F, P)**

However, various options were volunteered by participants on how to manage patients who had typical features normal inflammatory markers. Referral for specialist review was one strategy reported but often subsequent management very much depended on how 'convincing' the symptoms were and the level of confidence in the diagnosis.

> *"I'm probably more inclined to refer now. I've actually seen two people recently who I've referred – which is quite unusual having seen two in quite quick succession – who had reasonably convincing symptoms but their inflammatory markers were entirely normal. They fitted the right demographic and their symptoms were quite convincing but I wasn't convinced enough, so on the basis of normal inflammatory markers I've referred them to rheumatology"*
>
> **GP13 (5, F, S)**

Watchful waiting or a trial of treatment, if there was sufficient diagnostic confidence were other strategies employed when inflammatory markers were normal.

> *"I might give it a watchful waiting in that case, and, sort of, see how they go over the next couple of weeks or so. I may even repeat the bloods, because sometimes there's a bit of a lag isn't there? And I suppose if I'd got enough clinical conviction, and I couldn't think of anything else that I was missing, then I might go for a clinical, kind of, trial of steroids."*
>
> **GP 24 (12, F, S)**

The final feature that causes diagnostic concern surrounds a less than dramatic response to initial treatment with glucocorticoids which often leads to GPs re-visiting their original diagnosis.

> *"And occasionally also there's people who have a good response but not dramatic response and you start thinking about is this actually rheumatoid or some kind of inflammatory arthritis. And again we'll try and get someone clever on board but the problem is if they do have a response to steroids and don't like reducing them because their symptoms come back"*
>
> **GP16 (17, M, P)**

6.3.3.3 Contributors to diagnostic uncertainty

This theme concerns other factors that contribute to the diagnostic challenges associated with PMR. The two main subthemes that contribute to this theme adding to diagnostic uncertainty include "multi-morbidity" and "disorders that mimic PMR".

<u>Multimorbidity</u>

Multimorbidity is defined as "*the co-occurrence of two or more chronic medical conditions in one person*" [http://www.multimorbidity.net/, accessed 11/12/15]. Multimorbidity can impact on the challenge of diagnosing PMR in several ways, most notably when there is an overlap of symptoms (for example thyroid disease or osteoarthritis).

> *"I think it impacts at every stage, doesn't it? It makes diagnosis harder because people often have conditions where symptoms overlap and so it makes it harder to assess. If their function is limited by something else then the usual things you might look for are already affected by their other things, so you can't use your normal clues when going through their history. Often you see people who are on several other painkillers or who are maybe on steroids for something else, so it makes it difficult."*
>
> **GP12 (15, F, S)**

The presence of multimorbidity may also alter confidence for making the diagnosis. Given the long term treatment with steroids and the impact steroid treatment may have on

other conditions, GPs may become more reluctant to confidently make the diagnosis in people with multimorbidity.

> *"I think it makes my threshold for starting steroids a lot higher, and again I suppose that makes you want to be even more certain about the diagnosis, which I think is always just a difficult area really."*
>
> **GP13 (5, F, S)**

Disorders mimicking PMR

The differential diagnosis of PMR is extensive with a range of disorders that can present in a similar way to PMR. Guidelines advise clinicians to exclude GCA, infections and malignancy specifically, (amongst a long list of differential diagnoses) prior to diagnosing PMR. [Dasgupta et al 2010] Whilst easy to write in a guideline, excluding malignancy (for example) is extremely challenging, especially if the patient does not present any diagnostic clues.

There is clearly a certain amount of anxiety among GPs in missing the diagnosis. There is also an awareness that other disorders can mimic the symptoms of PMR. This lesson is often learned through previous experience.

> *"Other things you know occasionally something else will be going on and kind of odd rheumatological things kind of I don't know, where you've got cross over symptoms, vitamin D deficiency's one that I've found where someone, we live in the west of the country which is a bit cloudier and white people are getting significant vitamin D deficiency who don't go out very much and that can cause*

very similar symptoms. B12 deficiency again is something that I've picked up on the odd occasion and kind of I can't think now what the, how that's happened but I've certainly had to review the diagnosis."

GP16 (17, M, P)

Most participants had experience, or were aware of cases, where an alternative diagnosis to PMR was made, including serious/malignant conditions

"Yes, it does. And also ruling out other causes. I had a patient a few years ago who presented with really barn-door polymyalgic symptoms, with shoulder pain and hip pain, morning stiffness improved as the day goes on, raised inflammatory markers, normocytic anaemia, that all seemed very much like polymyalgia, improved within a couple of days of the steroids. But it seemed that she had a, sort of, paraneoplastic thing. She actually had a – oh, what do you call it? A 5HIAA secreting tumour, serotonin-secreting tumour. And so it was, like, paraneoplastic, and so that makes me also more reluctant to jump to a diagnosis of polymyalgia, because that did behave just as you would expect the polymyalgia to. It was just that we happened… It was difficult to try and find out the cause of her anaemia, which was presumed to be due to the polymyalgia, but then, because her iron levels were always normal, because of the inflammatory response. And so it made it very difficult, but within a couple of months we found out that it was actually more of an iron deficiency anaemia, and then she had the colonoscopy, and then that was how the diagnosis was made so, I'm always very, very vigilant with my

patients with polymyalgia, just to make sure nothing is going a bit awry, because other things can masquerade in a very similar way."

GP21 (7, F, S)

This awareness and fear of missing other diagnoses creates a certain level of vigilance and searching for other illnesses at subsequent follow up consultations.

"So I end up, every so often, doing a bit of an extended MOT on them, diabetes, you know, and just check their thyroids, because, as you say, a lot of them are on other things for other illnesses as well. And, yeah, often I see that the white counts have gone up a bit, so, you know, in the back of my mind there's always the horror of some kind of you know, a leukaemia type of thing."

GP22 (15, M, P)

6.3.3.4 Summary of findings relating to diagnosis

The diagnostic processes for PMR used by the GPs interviewed appear to be holistic and patient centred with a clear recognition of the complexities of this illness. A broad spectrum of experience was found among the GPs interviewed. Participants indicated that they were responsive to individual clinical presentations and aware of variety of ways that patients can present. Taking into account multimorbidity as a confounding factor when making a diagnosis was a key area identified as was concern about missing serious differential diagnoses such as malignancy. Guidelines can aid the clinician in making the

diagnosis but can potentially be over-simplistic giving the impression of a standard phenotype for PMR that is easily recognisable. For PMR however, and especially in general practice, where patients may present very early in the disease course, multiple consultations over an extended period of time are often required to build a diagnostic picture using a wide variety of clinical and laboratory features based on both experience and guidance.

6.3.3.5 Treatment and long term management of PMR

> *"They love it. They absolutely love it. They come back – and it's a really satisfying thing to treat, you know, if you've got the diagnosis right, and they come back a couple of days later and you should see it in their face, that they're absolutely transformed."*
>
> **GP22 (15, M, P)**

Treatment and long term management for PMR was identified from the cross sectional survey as the second most challenging area for GPs. Treatment is usually with prednisolone (an oral glucocorticoid), with current national guidance providing clear instructions in terms of initiating doses and the advised dose reduction regimen. [Dasgupta et al 2010] The two broad themes identified from the interviews concerning treatment are discussed in the following section. The predominant theme surrounded the "implications of treatment", will be discussed first. The second theme "practical

considerations" concerns more GP-related practical aspects of treating patients with PMR.

Implications of treatment

Several clear subthemes were identified relating to this theme, including the effects of treatment on patients, preventing and monitoring adverse effects and the impacts of treatment on existing co-morbidity. The lack of alternative treatment options was often also highlighted.

> *"The lack of other options, really……and that nothing else does seem to work particularly well for it, and you're a little bit stuck if, for any reason, they can't tolerate the steroids, and aren't getting on with them. You are a little bit stuck with what else to suggest. Yes, it's not exactly a nice option."*
>
> **GP24 (12, F, S)**

Adverse effects of treatment

GPs reported their own concerns surrounding the potential adverse events associated with the long term treatment with glucocorticoids, as well as concerns often expressed by their patients. Some participants had had patients that had experienced adverse events first hand.

> *"In terms of starting steroids, people in most cases don't seem too resistant to that idea initially. I suppose it's because they're in pain and they think it'll make them better. It's later on, when they're on them and getting side-effects, that they have*

more concerns about it [.....] Yes, I've certainly got a lady who developed diabetes for the first time whilst she was on steroids. Not by me, I saw her later down the route, but she had been started on them for PMR. Whether she was going to go on and develop diabetes anyway, she may well have done, but certainly she developed it whilst she was on the steroids. She's now off steroids but still on some low dose Metformin for her diabetes. She's still labelled as diabetic, which she certainly blames on the steroids. I think the other thing is GI side effects; that's what you actually see people complaining of mainly. Then weight gain is a big one"

GP13 (5, F, S)

However, whilst the potential adverse effects of glucocorticoid treatment are well known, participants weren't always specific about the problems that treatment caused nor were they entirely sure that the adverse effects were definitely related to treatment.

"but do you know I can't think off hand of somebody in whom I've thought well that's the cause of this. But then as you say it doesn't happen that often so maybe, I can't really think of instances where I've had, like I say there's just the sense of people that were quite well old people turning in to people who suddenly have a lot of problems and they're on more medication and they're just not as well at the end as they were at the beginning. But I don't know I think I am very negative about the diagnosis and so probably I am very negative about the treatment as well."

GP17 (11, F, P)

Prevention of adverse effects and drug prophylaxis

> *"So, then I say 'And here's another tablet for you. I'm sorry.' 'And, actually, here's a PPI [proton pump inhibitor (drug to prevent gastrointestinal complications)] as well.'"*
>
> **GP 24 (12, F, S)**

This sub-theme relates to efforts often made by GPs to try and prevent the development of adverse events using prophylactic medications. Currently national guidance recommends prophylactic treatment for patients at high risk of fractures due to osteoporosis and patients susceptible to gastro-intestinal complications.

> *"Yes. If I'm going to be committing someone to a long course of steroids, I will often start them on a PPI, to prevent them from getting gastrointestinal side effects. And, also, I often start them on a bisphosphonate as well, providing they're able to tolerate it, and calcium supplements."*
>
> **GP22 (15, M, P)**

There is a certain amount of confusion surrounding certain aspects of prophylactic treatment particularly surrounding osteoporosis prevention, especially as these medications are poorly tolerated. GPs seemed to take a more collaborative approach in deciding whether or not prophylaxis was appropriate involving patients, providing more information and possibly undertaking further investigations before making any final

decisions. However none of the participants indicated that they would use any formal fracture risk assessment for example FRAX or QFracture. [Kanis et al 2015]

> *"But, yes, of course. So, yes, so, you know, interestingly, whether to DEXA scan people or just treat them, I think our local guidelines say just treat. But I think I probably, personally, don't put people on something from the word go, because it seems all a bit, sort of, over the top to start on day one. So I think, in practice, I'd probably discuss it with them, you know, a month in, or maybe a bit more. Yeah. No, I do think I don't forget that, yes, in practice".*
>
> **GP12 (15, F, S)**

This reinforces the holistic approaches taken by GPs. Guidance can sometimes be very inflexible, yet treatment plans need to be individualised to account for multi-morbidity, multi-pharmacy, treatment risks and benefits and the patient's wishes.

<u>Impact of treatment on existing co-morbidity</u>

Barnett (2012) demonstrated that multimorbidity is significantly related to increasing age. Most of their sample over the age of 65, were suffering with multimorbidity. [Barnett et al 2012] Given that PMR occurs in older patients it is likely also that multimorbidity is common. Long term treatment with glucocorticoids may well result in significant adverse effects but could impact also on existing co-morbidity. Diabetes was the predominant disorder noted to be affected by concomitant treatment for PMR.

"Oh, definitely, yes, their diabetes control, definitely. I mean, they've usually got type 2 diabetes…so they don't run into any crises, but definitely, their diabetes control gets worse."

GP 24 (12, F, S)

Blood pressure control was a common disorder that was cited as being potentially affected by treatment although there was an awareness that the control of some chronic co-morbidities can deteriorate with time irrespective of treatment with glucocorticoids.

"I suppose it's a bit similar with blood pressure, isn't it? You see people who are already hypertensive and on treatment and then also on steroids. You see them and their blood pressure is a little bit worse and you think, Should I adjust their medication or as we're reducing their steroids should we just leave it and see? That's always another discussion with the patient, isn't it? I always feel a bit uncertain about how much of an impact the steroids are actually having, or whether the control is getting worse for whatever reason."

GP12 (15, F, S)

6.3.3.6 Practical implications of treatment and monitoring for PMR

This theme moves away from the direct consequences of treatment to the more pragmatic challenges that GPs face when treating PMR. The sub-themes are discussed in

the following sections and relate to the resource impact and follow up of patients with PMR and issues surrounding tapering and stopping treatment all-together.

Long term monitoring of PMR

Current guidance recommends a follow up plan for patients diagnosed with PMR and outlines aspects of care that should be monitored to exclude possible mimicking disorders and associations. [Dasgupta et al 2010] A clear challenge identified from the survey results surrounded the difficulties and resources needed for this, and was reinforced in the interview study.

> *"I think that clearly the initial diagnosis and the follow up can often be weekly for a bit isn't it, depending on the response and monitoring response, so depending on how well it's going in terms of rechecking inflammatory markers you're probably looking at the nurse doing that a couple of weeks down the line and depending if the sugars are going off that's going to throw in some more blood tests so yes, it is immediately creating a number of consultations with myself and the practice nurse really, yes."*
>
> **GP6 (20, F, P)**

Varying types of follow up were discussed by the GPs interviewed and this largely depended on the level of confidence that the GP had in their patient managing their own illness balanced against the perceived need for close monitoring by the GP for various

reasons including compliance, ability to self-manage and concerns about the original diagnosis. Unfortunately given the structure of practices, availability of appointments and sometimes unforeseen circumstances, patients are sometimes lost to follow up.

> *"Yes, again, sometimes people do get lost to follow-up, with all the will in the world, don't they? So I had one lady who had been seeing me very regularly. We were bringing it [steroids] down. Something else cropped up with her, and she ended up, sort of, seeing somebody else for a while about another thing. And then she just had been left on this dose of prednisolone"* **GP24 (12, F, S)**

Treatment dose tapering

The final sub-theme surrounds the process of slowly reducing the dose of treatment over time and was highlighted as a significant area of challenge from the PMR questionnaire survey. Although guidance on prednisolone tapering is presented in the PMR guidelines, [Dasgupta et al 2010] it can be challenging.

> *"Yeah oh definitely and then you try and get them off them and they get, I don't know it seems to me that they get very attached to the steroids in a funny way and they, if they start to ache again they come back and say oh I think I should increase my steroids which is maybe the right thing to do but it's just as I say woolly, oh I so dislike it."*
>
> **GP17 (11, F, P)**

Numerous approaches to the long-term and ongoing reduction in prednisolone dose were volunteered by interviewees. Some participants were very specific in terms of the way that they advised patients to wean down their glucocorticoid treatment.

> *"So if the patient is sensible I'll explain to them what I'm expecting to do with the reduction and often will then only follow them up, you know we have people book phone appointments and I'll tell them to book a phone appointment every eight weeks after an intervening reduction. And again if it's me and the patient that's fine, the problem comes where there are other people and you need to be very clear then if there's other doctors involved you need to be very clear about kind of making plans and making sure that the numbers are written down because otherwise you can have reducers plans but it's actually not very clear what the plan is and you know it's not always easy to pick up what those people are on."*
>
> **GP16 (17, M, P)**

Other GPs were less specific and allowed their patients to self-manage and wean their doses of prednisolone in a less formal way.

> "*I mean, I like my PMR patients because they are fairly straightforward. There's a kind of loose structure of reducing this drug, seeing how they respond. I will kind of go clinically; I don't push them to have blood tests every month. I mean, it just seems pointless. I judge their response by symptoms, not inflammatory markers."*
>
> **GP18 (22, M, S)**

"I've tended more to allow, the ones who can, to self-manage, and then just got them back for a review intermittently. I've not found any great benefit in bringing them back for frequent reviews when, especially if they're still working."

GP23 (12, F, S)

6.3.3.7 Summary of themes relating to treatment

It is clear from the interviews conducted that there are significant concerns surrounding the long-term treatment of patients who have PMR. This relates mainly to the potential adverse events associated with glucocorticoids and given that this is currently the only treatment option available to most GPs, it is an area of significant challenge.

A variety of approaches to on-going management were undertaken and volunteered by participants. Initial treatment is often very effective with patients responding with a significant and rapid improvement in most of their symptoms. However, on-going treatment becomes more challenging and has to be negotiated in order to balance the beneficial effects of the treatment (improved function) against the long term potential adverse effects, which become more prevalent with duration of treatment, and may need additional treatment to prevent/manage. The GP's interviewed tended to take a shared management approach that was individualised for each patient. GPs were aware of how the treatment could affect their patients given any co-existing morbidity and multi-pharmacy. They were also balancing confidence in the patient and the patient's own confidence to self-managing their illness with the additional burdens of compliance and adverse events of prophylactic treatments.

6.4. Challenges and influences impacting on the findings of the qualitative interviews

The following section briefly describes some reflections on the specific challenges encountered in conducting this qualitative study, including a discussion surrounding factors that may have influences on the overall findings and conclusions.

6.4.1 Practical Challenges

Recruitment

Recruitment was the main challenge encountered with this study. 61 (18.7% of the total number of study packs sent out) GPs returned responses agreeing to participate in the interview study. On trying to arrange an interview date, a further 16 GPs withdrew. A further 21 GPs were unable to be contacted despite repeated efforts. The study recruitment period ran from September 2014 to May 2015. This period included two parts of the year where GPs are particularly busy, Christmas and the closing of the financial year in April, where practice financial issues and enhancing the Quality and Outcomes Framework (QOF) assessments are made. This timing may have affected GP willingness to participate although the timing of the study was not intentional and it was not foreseen that recruitment to this study would take so long.

Furthermore time constraints on GPs may have affected recruitment. This was reflected by some of the interviews being undertaken in the evening and in the participants' spare time.

Finding a mutually agreeable time to conduct the interviews was at times challenging and in some cases had to be re-scheduled because of unforeseen events. To some extent, this had an impact on the time taken to complete all of the interviews.

Translating interviews into data for analysis (equipment failure)

Three of the interviews that were conducted were not transcribed. This was because the participants' voices could not be heard and was likely due to setting up the equipment incorrectly. Unfortunately the field notes did not contain enough detail to use them to contribute data to the study. After discovering this problem, the equipment was double checked by doing a testing check to ensure it had been set up correctly. The transcription services used for this study worked flawlessly and efficiently.

6.4.2 Factors that potentially influenced findings

Qualitative methods may be used to identify, clarify and explore areas of interest, possibly for further research. Qualitative methodology focuses on validity, credibility and methodological transparency in order to attempt to describe the truth. [Silverman 2010, Bazeley 2014] The following sections describe possible aspects of this study which may have influenced some of the study findings and have to be acknowledged.

6.4.3 Sampling frame

The sampling frame described in Section 6.2.3 was used in order to identify participants that would potentially convey data from a broad range of experience. Pragmatically, and owing to the poor response, interviews were conducted with anyone who agreed to participate irrespective of their underlying characteristics or experience. The characteristics of participants in medical survey research are reviewed in Chapter 4. It is likely that those agreeing to take part in further research on a particular subject followed by completing an interview will be highly motivated and interested in the subject, resulting in a highly selected cohort of participants.

The effect of the characteristics of "the volunteer" has to be considered as it can influence the data obtained and affect the conclusions made. Rosenthal investigated "the volunteer subject" and highlighted that volunteers tend to be better educated, more intelligent, more sociable and more conforming. [Rosenthal and Rosnow 1975] It became apparent during the interviews that some participants had clear PMR "intelligence", with experience and specialist interest in PMR and musculoskeletal disorders. However, this was certainly not a universal experience, with some GPs having a seemingly minimal awareness of the illness and others had apparently agreed to take part to express their discontent surrounding the poor diagnostic processes and lack of good treatment options for PMR. Whilst this group of participants may be highly selective they also are more aware of associated issues and so were ideal for the aims of this study in investigating the challenges associated with PMR.

6.4.4 Influence of the interview method on findings

A pilot interview was undertaken with a non-academic GP volunteer in order to determine potential technical issues with using the recording equipment and to gain feedback and advice from expert research supervisors on the conduct and performance of the interview. This interview was not included in the analysis. Several areas for improvement were identified. There was a tendency to over-explain and over-elaborate points which could be misinterpreted as critical of interviewee responses. To help with this, placing enquiries in the context of what other participants have been saying was a particularly helpful strategy to put participants at ease. There were also clear opportunities where I should have allowed the interviewee to fully talk and to avoid over talking.

The type of interview and the way in which an interview is conducted can have specific effects on the data obtained and this will be dependent on both the experience and skill of the interviewer and their perceived status. This was of a particular issue for this telephone interview study, given that the interviewer was both a peer and expert in the subject area. Participants who are interviewed by professional peers may feel that they are being tested or that their professional integrity is being scrutinised. [Coar and Sim 2006] However, interviews conducted by peers may also result in broader and richer accounts of clinical practice. [Chew-Graham et al 2002] As such, every effort was made to ensure that the participant did not feel judged. It was explained both in the participant information leaflet, and as part of the formal checking process prior to starting the interviews, that this was not a test of knowledge, but a discussion of experiences, and that honest views were being sought. On-going reassurance was provided throughout the

interview, whilst building rapport and empathically acknowledging shared personal challenges and experiences.

Given the volunteer status of participants that completed an interview, it is likely that this issue did not have a detrimental effect on the data gained from the interview. As identified by Chew-Graham (2002), an expert peer interviewer can also have its benefits and for this study it is particularly applicable as a background awareness of the issues allowed a focus and recognition of potential challenges to be explored reflexively and efficiently, given the limited time opportunity for interviewing. [Chew-Graham et al 2002]

One of the main criticisms surrounding telephone interviews is the obvious lack of visual cues that result from not being able to see the participant. For this study, it is likely that visual cues would not have impacted significantly on the data obtained. This is because of the type of data being sort that was largely factual and medically based often on personal experience with an expected level of intellect and background knowledge. Visual cues maybe important in studies where behaviour is being challenged or an in-depth exploration of a participant's experiences, knowledge or beliefs is being undertaken and visual responses may significantly add to the meaning of the data and conclusions. Equally for investigations of sensitive or traumatic subjects, rapport and visual encouragement may be essential to fully obtain the best data. However, a potential issue related to expert peers undertaking interviews may extend from the concept of social desirability bias where participants answer questions in the way that they think the interviewer wants them answered. For telephone interviews there is nothing to stop a participant preparing for an interview or having clinical guidelines available whilst doing the interview.

6.4.5 Analytical issues influencing findings

Some of the criticisms of qualitative research stem from the interpretive analytical techniques used. As such, qualitative analytical processes have been developed to try and improve the validity and reliability of the analytical process. It has also been noted that there are factors that can influence the data at the interview stage. For example the direction of the interview and the skill of the interviewer can affect the quality and or focus of the interview and subsequent transcribed data and so although the transcripts represent raw data at the analysis stage, the data may already be "*contaminated"*.

Analysing this data myself and having a significant prior knowledge was a potential issue with data interpretation in this study. Drawing on my experience as a clinical general practitioner and pre-identified areas of interest, significant analyser influences should be less of an issue but must be recognised and cannot be completely eliminated. The draw-back of having a pre-conception of the issues is the potential to miss important new information. However, a knowledge of the issues and a focus on those issues can improve trustworthiness.

Inter-rater analysis is a method that can be used to try and improve the reliability and trust-worthiness of the findings from analysis. Supervisors were given a copy of a transcript of an interview and asked to identify the broad themes that they felt were emerging from the interview. These were then compared with my own, although no formal inter-rater reliability analysis was undertaken. Studying inter-rater reliability can be helpful to ensure quality in the identification of broader themes, but is less reliable in demonstrating how these themes are developed and packaged. [Armstrong et al 1997]

In conclusion, eliminating all pre-conceptions in qualitative research can be challenging, and is not necessary. It is well recognised as an issue and is acknowledged here. However, for this study some of areas of interest were identified through data obtained from a national survey which informed and directed the interviews. The purpose of undertaking this qualitative study was to explore these identified areas in depth, and a pre-awareness of the issues, it may be argued, could enhance this by knowing when and where to explore issues and to help identify new and previously unrecognised problems.

6.5 Conclusion

> *"I think it can be managed in primary care, as long as there are sufficient resources out there; educational information and support in terms of being able to refer or to ask questions where there is uncertainty. I feel I've seen enough cases over the years not all diagnosed by me, because you obviously see people who are being treated for it more regularly than you see people on whom you've initiated treatment. I feel I've seen enough people where management seems to have been perfectly reasonable, where they've started on it with a good history and have got on fine and have reduced down and come off their steroids appropriately. I don't think it's necessary for all of those people to be seen in secondary care, but obviously the support does need to be there because there is a significant amount of uncertainty for quite a lot of people."*
>
> **GP13 (5, F, S)**

Successful diagnosis and treatment of PMR relies on an effective collaboration between patients and their GP, having a good understanding of the illness (both for doctor and patient) and appropriate access and follow up to ensure the right diagnosis and good on-going treatment concordance. As PMR does not have a gold standard diagnostic test, accurate diagnosis can take time, and varies with emerging symptoms, laboratory tests and the absence of red flag symptoms. This picture is somewhat at odds with a typical guideline that may give the impression that diagnosis and treatment is straight-forward and follows a set and clear pattern and can be achieved after an initial encounter and follow up with requested investigation results.

Generally participants felt that PMR should remain a predominantly primary care focused disorder providing there were the resources and access to specialist reviews if required. The GPs interviewed for this qualitative study appear to be alert to the common diagnostic pitfalls and challenges that PMR poses, taking a reflexive and holistic approach to diagnosis whilst being aware that other disorders can present in very similar ways, and acting accordingly. On-going treatment and monitoring is often undertaken in primary care, which is appropriate as patients potentially can have regular or rapid access to a clinician when problems arise. Patients can also be regularly monitored which, is less feasible for secondary care settings. Finally, as general practitioners are trained to and indeed do encounter a very wide spectrum of illness, they are well placed to recognise, manage and monitor any developing potential adverse events from treatment with glucocorticoids.

Chapter 7: Giant Cell Arteritis

> "*I don't think I have ever diagnosed it although I've looked at it a few times and again it's just horrifying isn't it because it's like polymyalgia except there's this fear about if you miss it then the patient will go blind and it will be your fault. But the same diagnostic problems [as PMR] and you send people for biopsies and it's a horrible thing to have done and then it's negative and then they say, oh but that doesn't rule it out and so you end up treating them anyway*."
>
> **GP 17 (11, F, P)**

7.1 Introduction

As highlighted in Chapter 1, giant cell arteritis (GCA) has a close association with PMR. Although not the main focus of the thesis, this chapter will briefly introduce GCA and illustrate its relationship to PMR. The remainder of the chapter will present GCA related results from both the GP National PMR questionnaire survey and the GP qualitative interview study.

7.2 History and background

Sir Johnathan Hutchinson has been attributed as the first clinician to describe a definite case of GCA in 1890 but it was not until the early 1930s that a case series with associated temporal artery biopsies and typical giant cell vascular infiltrates was formally described by Dr Bayard Horton. [Boes 2007] The potential association between GCA and PMR was

made in 1960 by Drs Paulley and Hughes in their description of a case series of 71 patients with GCA, 32 of which were described as having “anarthritic rheumatism”. [Paulley and Hughes 1960] More recent research has shown that up to 60% of GCA patients report PMR type symptoms during their illness with between 16 and 21% of PMR patients developing GCA. [Salvarani et al 2008] Gonzalez-Gay (2001) demonstrated that 9% of patients with isolated PMR had histological evidence of GCA on temporal artery biopsy. [Gonzalez Gay et al 2001]

Like PMR, GCA is rare in younger patients (<60 years old) and classically presents with features of new onset headache or head pain. This may be accompanied by jaw or tongue claudication. Visual disturbances, including amaurosis fugax and transient diplopia, are also associated and are signs of imminent visual loss which should be treated as a medical emergency. [Dasgupta (GCA) et al 2010]

Unlike PMR, GCA has more robust and accepted range of diagnostic tests that can be useful in making a definitive diagnosis. Temporal artery biopsy remains the gold standard diagnostic test with some studies demonstrating 100% specificity. [Vilaseca et al 1987] However its sensitivity is affected by the presence of “skip” lesions (sections of artery where typical histological findings are absent), the experience and technique of the surgeon performing the biopsy, the length of biopsy taken and the duration of treatment with glucocorticoids prior to the biopsy being taken. [Mahr et al 2006, Gonzalez Gay et al 2005] Temporal artery ultrasound is increasingly becoming recognised as a useful tool in diagnosis also, [Dasgupta (GCA) et al 2010] although to date it is not widely available in non-research settings. Table 7.1 summarises the clinical features of biopsy positive GCA and highlights the wide variation of symptoms with which patients can present.

Table 7.1. Clinical features of temporal artery biopsy positive patients with GCA

Clinical Feature	**Percentage of biopsy proven Cases with the feature**
Temporal Headache	52
Any Headache	76
Scalp Tenderness	31
Jaw Claudication	34
Any visual Symptom	37
Unilateral Visual Loss	24
Diplopia	9
Myalgia	39
Previous diagnosis of PMR	34
Weight loss	43
Fever	42
Absent temporal pulse	45
Any abnormality on palpation of the temporal artery	65
Erythrocyte sedimentation rate normal	4
Erythrocyte sedimentation rate greater than 50mm/hr	83

[Smetana et al 2002]

GPs remain the first point of medical contact for most patients. Given the risks of irreversible visual loss in patients in whom treatment is delayed [Ezeonyeji et al 2011] GPs need to be able to identify potential GCA patients early and initiate prompt, appropriate steroid treatment before referral for definitive diagnosis under specialist care.

7.3 Aims and objectives

The overall aim of this chapter is to describe the diagnosis, management and associated challenges of GCA in primary care. This will be achieved through the following objectives:

1. To investigate the clinical signs and symptoms used by GPs to identify GCA and any accompanying laboratory or imaging investigations used to confirm the diagnosis

2. To describe the usual management processes undertaken by GPs including initial treatment and associated specialist referral practices
3. To ascertain diagnostic and management challenges associated with GCA and to identify possible solutions to these challenges.

The methods used to achieve these objectives will be discussed in the following section.

7.4 Methods

The design and execution of the cross-sectional survey used to collect data on the diagnosis and management of GCA was described in Chapter 4. These questions included fixed response questions on management and general experience of GCA. The section also includes open response questions on signs and symptoms used to identify GCA, initial corticosteroid dosing and any associated diagnostic and management challenges encountered. The full questions can be reviewed in the PMR questionnaire in Appendix 3. The relevant domains are summarised in table 7.2

Table 7.2 Domains relating to GCA in the GP National PMR questionnaire survey

Question Number	Domain
18	Have you ever managed a patient with GCA?
19	What symptoms would lead you to suspect GCA?
20	What signs would lead you to suspect GCA?
21	Management and referral pathways for suspected GCA
22	Specialist to who suspected GCA patients are referred
23	Initiating dose of prednisolone

Within the qualitative phase of the study, GCA was included as described in Chapter 6.

Verbatim quotes, as in chapter 6 are labelled in the same way using the following key.

Key: [time qualified as a GP (years), gender (male/Female), seniority/role (S:salaried, L:locum, P:partner, SP: senior partner)]

7.5 Results

The following section presents the findings from the cross-sectional survey and qualitative study that are specifically related to GCA. Responder characteristics to the questionnaire survey and details of participants in the qualitative study were presented in Chapters 5 and 6. The results will be presented in a similar format to the PMR results under the broad themes of diagnosis and management and each result relating to the questionnaire survey will be referenced to the relevant question.

7.5.1 Identification and diagnosis

Although GCA is the most common large vessel vasculitis it is still a rare disorder and is infrequently encountered in general practice. Full time general practitioners can expect to see one case at most every one to two years. [Barraclough et al 2012] Of our survey responders only 879 (70.4%) indicated that they had managed a patient with GCA reflecting its rarity

Symptoms used to identify patients with potential GCA (Question 18)

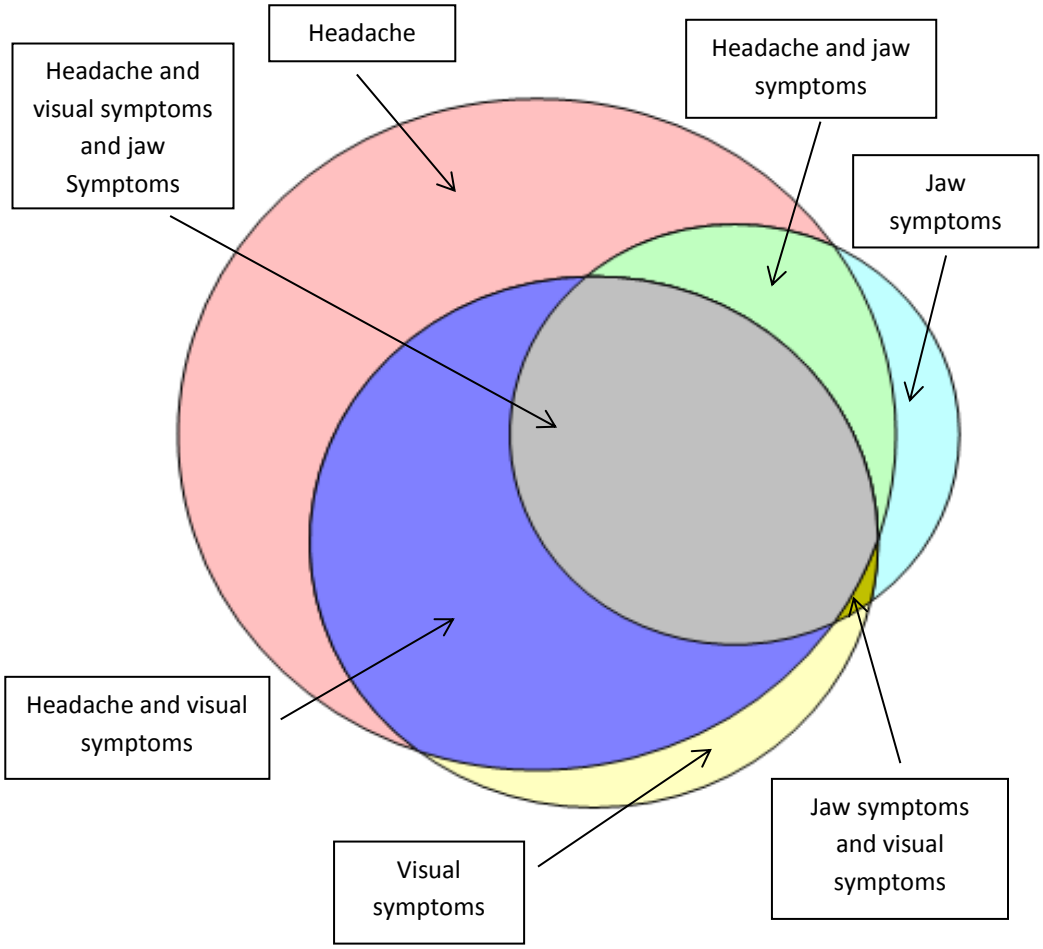
To ascertain how GPs were identifying patients with GCA a free text open response question was used to ask all participants to describe how they made a diagnosis of GCA. This question was analysed using quantitative content analysis, with the results summarised in Table 7.3.

Table 7.3 Table demonstrating the features used by responders to identify GCA

GCA Feature	**Theme Frequency**
Headache/Head Symptoms	1071
Visual disturbances	671
Scalp Tenderness	468
Jaw Symptoms	420
PMR symptoms	69
Systemic Symptoms	65
Fatigue	29
Joint/Muscle symptoms	20
Tongue symptoms	12

The predominant clinical feature used to diagnose GCA is headache, along with visual disturbance and scalp tenderness. Survey responders indicated that they often used a combination of features when making a new diagnosis. To illustrate this, the most commonly reported symptoms are presented as a Venn diagram in Figure 7.2, which highlights the overlap of the combinations of symptoms used to diagnose GCA. Of particular note was that 21.9% of responders indicated that they only use headache to identify GCA.

Figure 7.2 Venn diagram of symptoms used to diagnose GCA



7.5.2 Thematic analysis of qualitative interviews relating to GCA diagnosis

"I would say, a GPs role in this I think is in considering the diagnosis because you know you miss it [making a GCA diagnosis] in like about a fifth of them can go blind so you know my main thing is making the diagnosis."

GP7 (10, M, P)

Diagnostic confirmation through referral to specialists will be addressed in the later section which discusses the management of GCA. Two predominant themes surrounding GCA identification were identified. The first, “presenting features of GCA” is closely related to the second theme “fears of missing a diagnosis of GCA”

Presenting features of GCA

When asked about GCA symptoms in the interviews, participants often gave textbook descriptions of classical features of GCA.

> “*Well I mean again I'm looking for the headaches, the sort of cardinal signs, headache in someone over 55 you think giant cell arteritis really, that's my mantra, new different headache, classically unilateral but not always, focused around the temple, potentially some tenderness there, possibly protruding temporal artery, classically tender when they're combing their hair, but also looking for things like jaw claudication or tongue symptoms, it's not always the sort of classic but I've had someone with “oh my tongue just feels odd Doc” with or without PMR symptoms as well really and obviously the dread of visual disturbance as well really which can be anything really and can be very fleeting so I remember a patient that I had diagnosed had no visual symptoms at onset and then she rang a partner of mine at the practice and said I'd had just literally 10, 15 seconds of a sudden visual cloud and then gone again and actually she went on to get visual complications as well”*
>
> **GP6 (20, F, P)**

While textbook descriptions of classical GCA were given, there was recognition that some of these features may be difficult to recognise or link to GCA.

> *"jaw claudication is interesting, because I know at the time, my colleague and myself, kind of, looked a bit more up about GCA and he said, 'I've never heard of jaw claudication.' And, actually, I had, and will ask about it, but I'm not sure I've ever heard anybody say they've got it."*
>
> **GP15 (25, F, P)**

However some GPs highlighted how the wide range of symptoms associated with GCA meant that atypical presentations were not unusual.

> *"He came in before Christmas one year, probably about three or four years ago now, just with a vague headache, and hadn't had any visual disturbance at that point in time. And he didn't really have a lot of temporal artery tenderness. So, I said, 'Well, look. Let's try some ibuprofen or paracetamol,' you know. 'Come back in a week if it's not any better'. He came back in a week. It wasn't really better. We did some bloods at that point, and the ESR and CRP were normal. At the time he was already under the care of an ophthalmologist for something else, and a rheumatologist for something else. So, he had appointments with both of those departments, not specifically about his headache and, kind of, nothing different done. And he kept complaining about this, and then he lost his vision… I wrote in the notes at the time, 'Excludes GCA"……which, having read a bit more about it since, after this happened, doesn't totally exclude it. But he really didn't have any*

of the typical symptoms that would ring alarm bells. He wasn't, you know, tender or anything. And that was really upsetting for us all, I think, because, well, that's a devastating consequence isn't it? And, yeah, I think that really made us sit up and take note, and I'm quite sure we do more ESRs and CRPs than anybody else. And I'm quite sure we put people on steroids quicker, but perhaps bring them off steroids quicker, as well, if it doesn't, you know, if it doesn't solve the problem. I think it's made us a little bit, kind of, hypersensitive to the possibility. So, that's, kind of, what that one was about."

GP 15 (25, F, P)

Fear of missing case of GCA

Participants expressed considerable fear about missing a diagnosis of GCA as a missed diagnosis has the potential to result in irreversible visual loss which might be prevented with appropriate and timely treatment.

"*I find it, sort of, trickier, I think, to diagnose. I worry about it more. I worry about missing it. And I feel far less confident about treating it. I think when I was first qualified as a GP I think I thought somebody had got it every week. Anybody who'd got a headache, you know*"

GP 24 (12, F, S)

There is recognition that some of the symptoms of GCA can be non-specific, vague and occur commonly amongst patients in the older age group which can lead to diagnostic and treatment dilemmas.

> *"Well the most recent one that we went down this futile track was an elderly lady who was having headaches and kind of pain around her eyes and I'm trying to think what other symptoms she had, general misery really. And it sort of came and went and came and went and she didn't really have any visual problems which is good and when you said to her, "Does it hurt to chew?" she'd say, "Oh yes I think it does". And so yes all of that so in the end I started, I did discuss it with our local physicians because just in that situation where you don't want to miss it but on the other hand it doesn't seem like it's probably the most likely diagnosis. And we got as far as them saying, "Well if it's maybe a possibility then go ahead and treat with steroids", at which point she said, "No I'm feeling much better thank you". And that was that until she started complaining about it again another few months later"*
>
> **GP17 (11, F, P)**

Whilst participants seemed aware of the typical presentations of GCA, atypical presentations could result in referrals to the wrong speciality as GCA had not been recognised leading to delay in diagnosis.

> *"I had another one, a long, long, long time ago, you know, complaining of earache, and I referred him to Ear, Nose, and Throat. He reckons that he more or less said*

he was malingering. And then I did an ESR and it was something like 100 or something. And, you know, I think he responded quite well to steroids. But, again, it was 15 years ago. And he'd been going on for about a year or so, you know, to people. Yeah, and I think that turned out to be temporal arteritis."

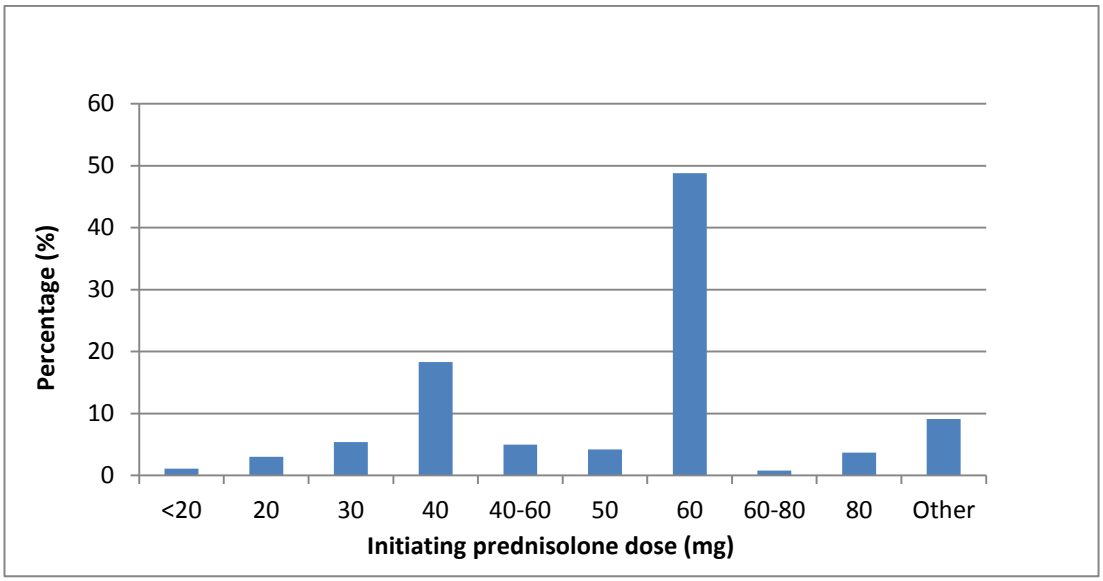
GP22 (15, M, P)

7.5.3 The management of GCA (Questions 20, 21 and 22)

For general practitioners, management is intimately associated with diagnosis as suspected GCA patients require urgent specialist referral for definitive diagnosis and treatment. [Dasgupta (GCA) et al 2010] However, key to the prevention of the visual complications of GCA, is the initiation of high dose glucocorticoids. Current guidance advises early treatment with 40-60mg of prednisolone and 60mg in the presence of ischaemic features whilst urgent admission for intravenous methylprednisolone is indicated in patients with threatened or evolving visual loss. [Dasgupta (GCA) et al 2010]

Figure 7.3 illustrates the initiating doses that responders indicated that they use in the initial treatment of potential GCA patients. As can be seen the most common initiating dose of prednisolone was 60 mg with 78.7% (n=983) indicating that they would initiate suspected GCA patients with an appropriate dose of prednisolone that was somewhere between 40 and 60mg in-line with current guidance.

Figure 7.3 Initiating prednisolone dose in suspected GCA



The graph indicates almost 10% of responders indicating an "other" dose. This was done for practical reasons as some responders indicated a dosing range (for example 30 to 80mg). Some responders indicated that they did not have a standard dose to mind as illustrated by the free text responses presented in Box 7.1

Box 7.1. Free text examples for other initiating prednisolone dose

1mg/kg - usually 60mg
Can't remember
High dosage would check with rheumatology
I would check local guideline
Need to look that up!
I would not initiate

Irrespective of the response to general practice initiated treatment, patients with GCA should usually be referred for specialist review and diagnostic confirmation. [Dasgupta (GCA) et al 2010] Table 7.4 outlines the usual actions of responders when faced with a patient with suspected GCA.

Table 7.4 Action taken by responders for cases of suspected GCA.

Action	n	(%)
Refer to hospital immediately without investigation	244	19.5
Do urgent blood tests and refer to hospital immediately if elevated	201	16.1
Do urgent blood tests, initiate steroids and refer for out-patients review urgently if blood tests positive	554	44.4
Do urgent blood tests, initiate steroids and refer for out-patients review routinely	66	5.3
Other	74	5.9

Responders indicated that they referred suspected cases of GCA to a variety of different specialties. Table 7.5 illustrates the various specialities to which potential GCA patients are referred by responding GPs whilst a few responders indicated that they did not refer patients at all.

> "*Do not routinely refer as no advantage gained in management usually.*"
>
> **Participant 3049 (23, M, P)**

Table 7.5 Table of specialties to which GCA patients are referred by participating GPs

Speciality	Frequency	(%)
Rheumatology	478	38.3
Ophthalmology	366	29.3
General Medicine	144	11.5
Accident and Emergency	35	2.8
Neurology	12	1.0
Elderly Care	9	0.7
Other	41	3.3

Whilst rheumatology was the most common speciality to refer suspected GCA patients to, Table 7.5 highlights that patients are being referred to a range of different specialities. This variation in specialty to which suspected GCA patients are referred probably reflects

regional variations in local policy and the availability of relevant expertise but may add to confusion for GPs unless referral pathways are clear.

Analysis of free text data

Qualitative content analysis of the free text responses relating to specialist referral revealed three notable themes.

The first theme surrounds non-emergency referrals and referral pathways to gain access to temporal artery biopsy. This most commonly included vascular surgeons but also, general surgeons, maxillofacial surgeons and ophthalmologists.

> *"This is a problem locally, I have found myself struggling to get a specialist to take responsibility. I try for eyes if eye symptoms and rheumatology if not but the need for temporal artery biopsy by a surgeon tends to cloud the issue"*
>
> **Participant 4161 (16, F, P)**

Secondly, for some, it very much depended on the presentation of the patient as to who they would refer to. Older patients may be referred to elderly care services whilst patients with visual symptoms would be urgently referred for immediate assessment to specialities according to local availability, usually ophthalmology or acute services such as accident emergency or acute medicine.

"this will depend on what symptoms dominate at presentation i.e. if acute visual loss….ophthalmology"

Participant 2645 (21, M, P)

The final theme surrounded the lack of an urgent and co-ordinated care pathway for patients with GCA, causing a potential delay in diagnosis.

"*Local issue regarding whether ophthalmology or vascular surgery will perform temporal artery biopsy, reliability of this procedure and steroid response whilst waiting for the biopsy"*

Participant 2506 (4, 2, P)

7.5.4 Thematic analysis of qualitative interview data relating to GCA management

Two main themes were found from the interviews and these relate to "Referral for definitive diagnostic confirmation by specialist" and "Initial and on-going management challenges". These themes largely echo the findings from the content analysis of the quantitative data presented above but provide more depth to these findings.

7.5.4.1 Referral for definitive diagnostic confirmation by specialist

Issues related to specialist referral was the dominant and recurring issue relating to GCA expressed by the general practitioners interviewed. Several sub-themes were identified

relating to which speciality the patient was referred, the process of arranging a temporal artery biopsy and the timeliness and other issues surrounding biopsy.

Speciality to which suspected GCA should be referred

For this sub-theme, there was clear regional variation in how and to whom suspected GCA patients were referred. For some participants the referral route was well established.

> *"If their history was suspicious and their inflammatory markers were raised, I would then contact…well we've had this issue between rheumatology and ophthalmology and who to contact, and the line seems to be that if they've got any visual symptoms then they go to ophthalmology and if they haven't then they go to rheumatology. But I would certainly discuss it that day if I thought somebody did have it."* **GP13 (5, F, S)**

However for some respondents in other regions it was less clear as to how or to whom suspected patients with GCA should be referred.

> *"But, generally, you speak to the on-call medical team, and they will advise me to speak to someone else. And then they advise me to speak to someone else. So you end up making loads of phone calls to try and find out which route you go in, which is frustrating and time-consuming."*
>
> **GP21 (7, F, S)**

Arranging temporal artery biopsy

Several participants reported that when they suspected GCA the GP was expected to arrange the temporal artery biopsy. However, this was not always straight-forward, with often varying specialities performing the biopsy.

> *"we would try and get a temporal artery biopsy fairly promptly. It has been a bit difficult in the past, and you know, you're supposed to get it done within a day or two. We traipse round the ophthalmologists, who say, 'No, speak to the vascular people.' Who say, 'No, speak to the general surgeons.' Well, we tried, initially, referring to the ophthalmologist, and they just aren't keen at all. So, at the moment we've had, a general surgery team who have done a temporal artery biopsy for us, and the vascular surgeons have. But our local vascular surgery team is now in *******, which is quite some way away. So, again, if that situation crops up, I think we'd try the general surgeons first and see if they would do that. But it still took a week, from us seeing a patient, to getting the temporal artery biopsy, last time it happened. And you've, kind of, got to make a decision by then, haven't you?"*
>
> **GP15 (25, F, P)**

Challenges surrounding the urgency for GCA patients having temporal artery biopsy

Most GPs interviewed considered GCA to be a medical emergency. However, this was not always reflected by local referral policies.

"you refer them under a two-week wait, and it's not that much of an emergency, whereas we all thought you referred them acutely, because it was that much of an emergency. So there was a big discrepancy of views between what we felt we'd been taught about it, and what other people were now doing."

GP23 (12, F, S)

Equally there was recognition that some patients had been experiencing symptoms for some time before a diagnosis is made without coming to harm, resulting in participants questioning how urgent referrals need to be and how quickly treatment needs to be initiated.

"I know we, kind of, all get it drummed into us, you know, we should all get these things sent in on the day. But I think, well, one of them was hanging round for a year, and he didn't really come to any harm, except undue pain and distress that he had. And the other one was hanging round for a couple of months, you know. And they were both proved – as I say, I'm turning the clock back 15 years - but I think they were both proven to be temporal arteritis. It maybe isn't that, kind of, you know, you must get them in on the day, as I thought as a medical student, you know"

GP22 (15, M, P)

Delays in patients being seen by specialist services, given that GCA is considered a medical emergency was a recurring issue with confusion surrounding to whom patients should be referred and who would take ownership and responsibility for definitive care. For most GPs, this related to initial diagnosis and often created dilemmas surrounding decisions on initial treatment.

> *"And, certainly, in the past, twice that I've done it, in the past couple of years, we've started them on steroids first, because, kind of, getting anybody to see them quickly, you know, within a day or two, not been possible, which doesn't seem very ideal to me. And we've taken the view if it turns out to be wrong, we can stop it, but if we don't start it, there might be a problem before they get the biopsy. So that's, kind of, what we've done here."*
>
> **GP15 (25, F, P)**

Delays in specialist assessment also created confusion around the likelihood of a positive temporal artery biopsy, especially when treatment had been initiated.

> *"The patient that I referred on the NHS, she ended up having a biopsy before she saw a consultant rheumatologist. So, yes, it was done that way round. The biopsy, of course, came back negative because the two week delay before getting it done meant the steroids had treated it. So, I mean, obviously, you can get the negative biopsies because of the nature of it all, but she had pretty convincing symptoms, and I'm pretty certain that, if the biopsy would have been done at bit earlier, it would have had a better chance of yielding a positive result. And the other patient*

who went privately, he got his biopsy done within a couple of days of starting the steroids, it came back positive".

GP21 (7, F, S)

Delays in patients being reviewed by specialist services had for some resulted in no biopsy being done at all, creating great uncertainty and cautious reduction in treatment.

"what then happens in secondary care, it's less than ideal, they seem to rotate who might do a temporal artery biopsy between vascular ophthalmology and general surgery I think and they see to it on a sort of rotation but it all feels a little bit hit and miss really but the patient generally is having that temporal biopsy before ever seeing a rheumatologist and the timeliness of that temporal artery biopsy is not ideal so the most recent patient where there was diagnostic uncertainty I had actually, she had raised inflammatory markers, she had a headache but was fit but not a great response to steroids after about a week so I had a phone conversation with the rheumatologist who said refer her up, we'll get a temporal artery biopsy, the date for that just missed the window by two or three weeks to the point where it was not going to be a useful process to put her through so she didn't have that, then she got seen in clinic some weeks later by which time I'd had further telephone conversations with rheumatology and we were starting to tail her off the steroids really but very slowly because of the diagnostic uncertainty so yeah, not ideal."

GP6 (20, F, P)

There were doubts expressed by participants about the benefit of doing a biopsy at all given that a negative result does not entirely exclude the illness, due to the presence of skip lesions and that patients may be unwilling to undergo an invasive procedure.

> *"I suppose, that you do the biopsy because it doesn't really change the management much because if it's negative, I suppose you could potentially wean down the steroids faster but if it's there, you're going to continue the steroids."*
>
> **GP19 (8, F, S)**

No GPs interviewed demonstrated any awareness of the possibility of temporal artery ultrasound as an alternative to biopsy. Although it was not a specific topic for discussion, it may represent an effective investigation given its non-invasive simplicity which will benefit patients who cannot undergo biopsy.

7.5.3.2 Initial and on-going management of GCA

Two main sub-themes were identified surrounding the initial and on-going management of GCA. The first sub-theme surrounds the initial treatment with prednisolone. The second larger sub-theme relates to the on-going management.

Initial treatment with glucocorticoids

Guidance suggests that "*high-dose glucocorticoid therapy should be initiated immediately when clinical suspicion of GCA is raised"* usually with a dose of between 40 and 60 mg of prednisolone. [Dasgupta (GCA) et al 2010] Some GPs indicated that they would start treatment themselves.

> *"Okay so I've had the conversation with them already that the worrying feature of this condition is visual loss so I give them lots of safety netting about how to deal with that and I am then involving secondary care so I'm keeping them on 40mg and I'm involving secondary care"*
>
> **GP6 (20, F, P)**

Others however would gain specialist advice prior to initiating treatment. The reasons for this were not always clear, but were often because it had been a long time since the GP had seen a case and confidence in management may have been low.

> *"I think the rheumatologists would say start the 60[mg] and I will see them in clinic."*
>
> **GP4 (6, M, P)**

Given the rarity of the disorder though, some GPs could not remember the initiating dose and indicated that they would have to look it up.

"I would probably look up the current guidance and find out what sort of duration of steroids is recommended initially and go from there but yeah, I would definitely – if I had a patient acutely, I would have to review that."

GP19 (8, F, S)

<u>On-going management</u>

Several issues regarding on-going management were identified from the interviews. Like PMR there were concerns regarding the adverse effects of long term treatment with glucocorticoids. These concerns were greater for GCA compared to PMR given the higher doses suggested for treatment.

"Well, it's a good two years of treatment with steroids and all the complications and side effects that they carry with them. So, yes, and high doses of it, which have been poorly tolerated with the patients. [.....] One patient, she had diabetes, and she was started on the steroids, and she was struggling with awful side effects from the steroids. She developed, well, lots of depressive symptoms. Her blood sugars went all over the place. She got a lot of pitting oedema of the legs, which was hampering her mobility. She got unsteadiness due to the steroids. She got all sorts of side effects. So it does make me, after seeing patients like that, more reluctant to just jump in and start on the steroids, because you're committing to such a long course of treatment."

GP21 (7, F, S)

The on-going management of GCA patients is usually shared between specialists and GPs (when compared to PMR which is mainly managed by GPs). The amount of specialist follow up will depend on any associated complications of the disease such as visual impairment or clinical comorbidity. Unfortunately in some cases, this resulted in a blurring of who was responsible for the patient leading to confusion.

> *"Yes again just I think in terms of the ongoing management really because my experience with another patient, the one that ended up with visual disturbance, she sort of then fell between ophthalmology and rheumatology without either necessarily taking full responsibility for her and actually she was a patient of a partner of mine so he was kind of following her up but his experience was that he was piggy in the middle really, the patient on 60mg of prednisolone, herself quite confused as to who was taking responsibility for sorting her out really so again it is the secondary care element of this is difficult, yeah…"*
>
> **GP 6 (20, F, P)**

7.6 Discussion

Baseline characteristics, issues surrounding recruitment, bias, challenges and other aspects that relate to both the cross sectional survey and qualitative study described earlier in chapters 4, 5 and 6 apply equally to the results found for GCA as the data was obtained from the same participants and so will not be discussed again here.

The diagnosis of GCA can be challenging especially in view of the rarity of the disorder and the wide variation in its presentation. It appears that GPs responding to the survey

rely overly on headache when diagnosing GCA. Given that almost half of patients do not present with a classical temporal headache and that 24% of patients with proven GCA have no headache symptoms at all, [Smetana et al 2002] excluding GCA on the basis of no headache has the potential to miss a significant proportion of patients with GCA. Some symptoms, like headache, are common [Boardman et al 2005] with over half of over 65 year olds having had a headache in the previous 12 months, [Prencipe et al 2001] but serious pathology is rare in general practice. For some participants their usual practice had been affected by experiences where GCA patients had had unfavourable outcomes [GP15]. Indeed for some participation in the qualitative study may have been an attempt to voice disquiet about adverse experiences that they had had.

The group of patients with no headache are recognised to be at higher risk of permanent visual loss as a result of delayed diagnosis. [Ezeonyeji et al 2011] Therefore, if alternative presentations are not recognised by GPs they will continue to remain a high risk group. Educating clinicians about other presenting symptoms and atypical presentations is essential to optimise diagnosis and reduce delays in instigating appropriate treatment and referral, which could reduce the potential for visual loss and serious long term complications for this patient group.

The initial referral is critical and identifying patients with GCA and not missing the diagnosis was a predominant theme amongst the GP responders. However, the dominant issue that came from the data is what happens once a suspected GCA, patient has been identified. There are great regional variations in practice with regards to who GCA patients are referred, how definitive diagnosis is made and who arranges and performs

temporal artery biopsy. Streamlining patient pathways would reduce the diagnostic confusion and perhaps improve outcomes for patients

Whilst the majority of responders seem to be prescribing appropriate doses of glucocorticoids to patients with suspected GCA the subsequent management is more variable. Rheumatology remains the predominant speciality to whom GPs refer, however some responders indicated that there do not appear to be robust clinical pathways for patients who have been identified with possible GCA and need further specialist follow up. Given the rarity of GCA and variation in its presentation, the potential for misdiagnosis is high. In regions where temporal artery biopsy is arranged by the general practitioner or undertaken before seeing the relevant specialist there is the possibility that a significant amount of unnecessary biopsies are being performed that could be avoided if patients with suspected GCA are reviewed first by a clinician with significant experience in diagnosing and identifying suspected GCA. No participant discussed temporal artery ultrasound. Further studies will be needed to determine whether availability and accuracy of temporal artery ultrasound will alter requirements for biopsy. However, it may be a preferred option for those with significant co-morbidities or too frail to undergo biopsy. Additionally, it is less invasive and would be more conducive to being embedded in an acute care pathway for the rapid assessment of GCA.

Delays in assessment for definitive diagnosis, creates several conundrums surrounding initial treatment. Current guidance is clear that treatment should not be delayed and should be initiated in all patients with suspected GCA although the sensitivity of temporal artery biopsy declines the longer treatment has been given before biopsy. [Pieri et al 2013] Additionally the American College of Rheumatology criteria for GCA suggests that a

positive temporal artery biopsy is not essential to diagnose GCA. [Hunder et al 1990] High dose glucocorticoid treatment may have a significant impact on symptoms by the time they present to the reviewing specialist and therefore definitive diagnosis for patients who have had a negative biopsy is extremely challenging. Accurate diagnosis is critical however. A decision to stop treatment in patients with true GCA could result in visual loss but equally a decision to continue treatment in someone who does not have GCA will expose that patient to an inappropriate prolonged treatment course with glucocorticoids and all its associated potential adverse effects. Pieri (2013) demonstrated that in almost half of patients with suspected GCA, treatment was continued despite a negative temporal artery biopsy. [Pieri et al 2013]

The quantitative data suggested that almost half of participants would not initiate treatment prior to referral. However, not initiating prednisolone may be in part a matter of local policy rather than poor or inappropriate GP management.

> *"Locally this gets referred to ophthalmology[…..] and our practice is actually within the grounds of the hospital so we've got no issues really in terms of administering steroids you know before they were seen, they would be seen within an hour by an ophthalmologist. But I'm aware that if I worked in another place that waiting for an assessment by an ophthalmologist you shouldn't delay the administration of sort of high dose steroids."*
>
> **GP 7 [10, M, P]**

Whilst an increased focus on education and awareness of GCA (given its rarity and the range of presenting features that GCA may present) may aid better identification of potential GCA patients, significant challenges with GCA remain in primary care, some of which need to be addressed in conjunction with specialist settings. Guidance advises that GCA is a medical emergency, yet there are regions in the UK where specialists local policy or referral pathways do not reflect the same urgency. This dissidence clearly causes confusion and conflict in GPs decision making which could unfortunately result in a less urgent approach by GPs resulting in potential adverse outcomes for patients with GCA.

The question of the effect of glucocorticoids on the sensitivity of temporal artery biopsy and newer and experimental imaging modalities like ultrasound and PET scanning remains controversial. A pragmatic way to eliminate this issue would be to undertake these further investigations as an emergency prior to treatment or within a minimal time frame after initiating therapy. Also, the availability of related specialist services may not exist in all regions, particularly in more remote areas. However, in order to improve outcomes for potential GCA patients, robust and nationally accepted standard referral pathways need to be developed and in place for effective onward investigation and timely management.

This qualitative study was undertaken as part a wider project of two complementary studies investigating PMR. The wider conclusions of this study will be discussed in conjunction with the questionnaire survey in Chapter 8.

Chapter 8: Summary of thesis conclusions and areas for future research

8.1 Introduction

The overall aim of this PhD was to describe the current diagnostic and management practices used by general practitioners caring for patients with polymyalgia rheumatica (and the allied condition giant cell arteritis), to identify the barriers to effective care and determine targets for future interventions and educational initiatives that could lead to improvements in patient care. This chapter summarises the main findings of the thesis, discusses the implications of these findings for clinical practice and makes suggestions for further research.

8.2 Summary of key PMR findings

The systematic review (Chapter 3) highlighted the lack of primary care focused research, identifying a range of PMR studies conducted predominately in secondary care settings and on highly selected patient populations. Despite emerging evidence on the role of biomarkers and imaging, making an accurate diagnosis is still dependent on identifying the classical cluster of clinical signs and symptoms described in published classification criteria.

Current clinical practice was investigated using two complementary methodological approaches, a large cross-sectional survey (Chapters 4, 5 and 7) and semi-structured interviews of general practitioners (Chapters 6 and 7). Whilst GPs reported using well recognised features of PMR to make a diagnosis they found the condition challenging, especially when it presented in an atypical way. Misdiagnosis was a recurring concern,

with GPs anxious about alternative (and more sinister) diagnoses and the implications of inappropriate treatment with glucocorticoids. Despite this, adequate exclusion of alternative diagnoses does not routinely happen in UK primary care, representing a missed opportunity to improve clinical care. Likewise, there was limited awareness of the full range of investigations that are suggested in current guidance [Dasgupta et al 2010] prior to making a diagnosis of PMR, with an over reliance on the role of inflammatory markers.

Despite response to glucocorticoid treatment not being included as part of the classification criteria for PMR, GPs still rely on this feature when making a diagnosis. Doses of glucocorticoids prescribed are frequently not in line with national guidance, with 40% of GPs using higher than recommended doses.

Whilst many chronic diseases (e.g. diabetes, asthma) have well formulated systems for on-going medical review, this does not appear to be the case for patients with PMR who frequently suffer from a lack of coordinated or structured follow-up. This not only impacts on treatment for PMR but also presents challenges for medication titration and for active surveillance of both the disease its sequelae (e.g. coronary heart disease) and its adverse treatment outcomes (e.g. diabetes, hypertension, and osteoporosis). Despite guidelines advocating frequency of follow up for PMR patients this study would suggest that a more structured follow up with glucocorticoid tapering and active surveillance for common complications could improve outcome for PMR patients.

8.3 Summary of GCA findings

Findings from the cross-sectional survey and semi-structured telephone interviews illustrated the challenges faced by general practitioners diagnosing and managing patients with GCA. GCA is a diagnosis that GPs worry about missing, because of the risk of serious adverse long term patient outcomes in cases with diagnostic delay or where the diagnosis has been missed. Whilst GPs were comfortable with classical presentation patterns, they over relied on headache as a trigger to diagnose and had limited awareness of the full range of symptoms associated with GCA. Current clinical guidelines and treatment recommendations were not widely known, with a significant proportion indicating that they would not routinely initiate treatment with high dose glucocorticoids before a specialist diagnosis was made. This however, may in part, reflect varying regional policies and care pathways. In general, GCA was not viewed as a medical emergency, with regional referral pathways being highly variable and difficult to navigate.

8.4 Clinical Implications and research recommendations

This PhD has highlighted a number of implications for clinical practice, many of which have associated research recommendations. These are discussed in the section below.

8.4.1 Improving the diagnosis of PMR and GCA in primary care

Diagnosis of both PMR and GCA are challenging in primary care. Both conditions are relatively unusual and as such it is currently possible for general practice trainees to not have any exposure these patients during their training. Furthermore, specialist placements in rheumatology in vocational training programmes and exposure to musculoskeletal training in traditional 'half day' release programmes is patchy and suboptimal [Warburton, personal correspondences December 2015]. The findings from both the cross-sectional survey and semi-structured interviews highlight the need for improved education into the management of these neglected and often sub-optimally managed conditions. Current clinical guidelines are published in high impact speciality journals including Rheumatology (British Society for Rheumatology guidelines), Annals of the Rheumatic Diseases and Arthritis and Rheumatology (joint European League Against Rheumatism and American College of Rheumatology guidelines). GPs have limited awareness of these publications and often have limited access to the articles published in them. I have been active in trying to improve the dissemination of high-quality evidence into clinical practice, authoring a brief guideline summary on PMR [Helliwell et al 2012] and co-authoring a similar article on GCA [Barraclough et al 2012] both of which were published in the British Journal of General Practice, a journal that is distributed monthly to all members of the Royal College of General Practitioners [Appendix 7]. Furthermore, I have written a book chapter on 'PMR in general practice' (Oxford University Press, release date Easter 2016), co-authored an Arthritis Research UK 'Hands on' guide to PMR which was mailed to all general practitioners in the UK [Appendix 8] and helped to develop the 'Map of Medicine' for PMR. Whilst these initiatives are no substitute for high quality and

on-going clinical education, they demonstrate my ongoing commitment to improving care for patients with PMR and GCA and highlights the willingness of journals and publishers to further knowledge in these areas for GPs.

Some areas where future educational initiatives could be targeted need to be informed by research. Whilst it is evident that patients presenting with classical symptoms are diagnosed relatively quickly, there is a lack of awareness of atypical presentations. These potential presentations are highlighted in clinical guidelines, but many of these symptoms are vague and not specific. Future work quantifying the predictive value of individual and groups of symptoms could improve diagnostic accuracy and support GP decision making. This would help with the over reliance GPs have on certain characteristics such as headache (for GCA) and response to glucocorticoids (for PMR).

GPs responding to both the cross-sectional survey and participating in the semi-structured interviews highlighted the need for improving diagnostic technology, expressing the lack of a 'gold standard' test as a key barrier to effective management. Further research is needed in this area which should be particularly focussed to a primary care setting, where patients will have a different spectrum of clinical symptoms. One potentially important innovation is the introduction of ultrasound, yet to date the utility of this modality has not been investigated in a primary care setting. Consideration also has to be given to the availability of laboratory tests and or imaging for use in primary care as some biomarkers may not be readily available and the availability of high-quality musculoskeletal ultrasound is limited in primary care and as such it is unlikely to have a major impact on clinical care in the foreseeable future.

Existing classification criteria have been extrapolated into proxy diagnostic criteria for clinical use but there are several issues surrounding the use of classification criteria for clinical practice. Classification criteria are designed to identify a standard patient with a high probability of PMR for research purposes, and as such do not account for patients with co and multi-morbidity, polypharmacy and atypical presentations, all of whom are managed in primary care. Further research is needed to support GPs in making an accurate diagnosis in a "real-life" primary care population rather than an 'artificial' research setting.

Response to treatment with glucocorticoids remains controversial yet it is clear that GPs rely on this feature when assessing accuracy of diagnosis. Recently published classification criteria suggest that treatment response should not be relied upon when classifying PMR for research purposes, [Dasgupta et al 2012] yet the majority of patients included in this study were from secondary care. This patient group typically represents diagnostic uncertainty or lack of response to treatment, hence the need to refer to secondary care. Response to treatment could be a useful diagnostic aid in primary care, yet to date this has not been formally evaluated. One approach that has been advocated is the use of 'steroid sandwich' in which patients receive glucocorticoids in week one, placebo in week two and glucocorticoid in week three. [Quick et al 2012] This allows a more objective assessment of response to treatment.

8.4.2. Improving the management of PMR and GCA in primary care

Guidance on glucocorticoid treatment is conflicting, with different clinical guidelines providing different advice. Furthermore, guidance is based largely on expert secondary care consensus, rather than high quality research evidence. Recently published guidance from the ACR/EULAR advocate using a minimum effective initiating dose of glucocorticoid of between 12.5mg and 25 mg of prednisolone, with precise dose being guided by the presence of other morbidities, risk of relapse and risk of adverse effects. [Dejaco et al 2015] Such a wide dosing range is likely to cause confusion rather than reassurance to clinicians. 40% of responders to the questionnaire postal survey indicated that they were initiating PMR patients on doses of prednisolone of 30mg or more, a level that is highlighted in the guideline as being inappropriate. [Dejaco et al 2015] It is unclear why this dose of prednisolone is being used and no research has ever indicated that this was an appropriate dose to use with Boyle and Beaty (1961) advocating low dose glucocorticoids over 50 years ago. [Boyle and Beaty 1961]

Evidence on the optimal dosing regimen, and the associated titration in response to treatment, is largely based on limited, low quality, secondary care trials. There continues to be a need for a large pragmatic primary care based trial to provide GPs with the evidence needed to optimise the management of PMR patients.

For many patients, PMR and GCA represent a long term condition, yet many GPs do not recognise or treat these diseases in this way. Optimal management of long term conditions requires patient self-management supported by regular monitoring from health care professionals. For PMR and GCA this is especially important, as patients not only risk long term consequences from their PMR/GCA (e.g. vascular disease, visual loss)

but also adverse events (e.g. osteoporosis, hypertension) related to their treatment. Such concepts are currently lacking in clinical guidance but are a core feature of high quality primary care. General practice needs to develop systems to support integrating new innovations into patient care and to support patients to self-manage. Asymptomatic patients could be provided with clear instructions and supported to reduce glucocorticoid dose and to monitor for potential side effects and complications. Many long term diseases (for example asthma and diabetes) are monitored by a wider multidisciplinary team including practice nurses using standard structured assessments and associated input from doctors when needed. This approach could be implemented for intermittent follow up and monitoring of PMR patients to ensure continuity and to achieve a standard of best practice.

The cross-sectional survey and semi-structured interviews highlighted the lack of consistency in referral pathways and the problems GPs face when trying to refer to appropriate specialist care. One recommendation to improve care for patients with GCA would be the introduction of a nationwide standardised fast-track pathway for patients with suspected GCA. [Patil et al 2015] Patients would be able to access appropriate diagnostic tests (e.g. ultrasound, temporal artery biopsy) and have improved confidence in the accuracy of their diagnosis. Key windows of opportunity exist for patients with GCA. The accuracy of temporal artery biopsy reduces with increased duration of glucocorticoid treatment making prompt assessment important. Fast track pathways have already been introduced in some parts of the country (e.g. Southend, Bristol). Lessons in introducing fast track pathways can be learnt from other important areas, such as the two week wait referrals currently used to improve cancer care. One key feature that is important to

consider is the sensitivity and specificity of symptoms triggering referral. More work is needed in this area, as the predictive value of many GCA symptoms is currently unknown. Future research developing a risk prediction score (such as the Wells score currently used to predict the likelihood of deep vein thrombosis and pulmonary embolism) would be beneficial to primary care.

8.5 Conclusion

PMR and GCA remain challenging disorders and whilst medical technologies have progressed and can contribute to more effective processes of exclusion of mimicking disorders, the diagnosis of PMR and GCA still relies largely on the clinical expertise of the diagnosing physician. For the majority of patients initial identification and long term management of PMR and GCA will be undertaken by their GP. Whilst this thesis contributes to the research evidence, a concerted focus of further research in this setting is needed in order to improve diagnosis and outcomes for patients.

> *"Polymyalgia rheumatica remains an enigma, one and one quarter centuries after its first recognisable description in a medical publication It is now known that it is more common in women than in men; there is a dramatic response to corticosteroids and there is clear evidence of synovitis, bursitis and tendinitis in the proximal limb girdles. Apart from these few additional facts, almost nothing has been added to the astute clinical observations about the disease by Bruce in 1888."*
>
> **[Rooney 2014 p225]**

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Appendix 1 Search terms for Medline and Embase and search history for the literature review of diagnostic and classification criteria for PMR and their use in clinical practice

Medline

1. Polymyalgia Rheumatica/

2. polymyalgia.mp.

3. (senile adj2 gout).mp.

4. (rheumatic adj2 gout).mp.

EMBASE

1. exp rheumatic polymyalgia/

2. (polymyalgia adj2 rheumatic$).mp.

3. (senile adj2 gout).mp.

4. (rheumatic adj2 gout).mp.

Search History:

1. MEDLINE; POLYMYALGIA RHEUMATICA/; 2057 results.

7. MEDLINE; CLASSIFICATION/; 8375 results.

8. MEDLINE; exp BOOK CLASSIFICATION/ OR exp CLASSIFICATION/ OR exp INTERNATIONAL CLASSIFICATION OF DISEASES/; 122178 results.

9. MEDLINE; (classification AND criteria).ti,ab; 16448 results.

2. MEDLINE; (polymyalgia AND rheumatica).ti,ab; 1878 results.

3. MEDLINE; polymyalgia.ti,ab; 2019 results.

12. MEDLINE; (diagnostic AND criteria).ti,ab; 48001 results.

13. MEDLINE; "diagnostic criteria".ti,ab; 25551 results.

14. MEDLINE; exp DIAGNOSIS/; 6043572 results.

15. MEDLINE; 12 OR 13 OR 14; 6065754 results.

16. MEDLINE; criteria.ti,ab; 310343 results.

5. MEDLINE; (rheumatic adj2 gout).mp; 23 results.

18. MEDLINE; 6 AND 11; 21 results.

19. MEDLINE; 6 AND 15; 1307 results.

20. MEDLINE; 6 AND 16; 132 results.

21. MEDLINE; 19 [Limit to: English Language and Humans and (Age Groups All Adult 19 plus years)]; 735 results.

6. MEDLINE; 1 OR 2 OR 3 OR 4 OR 5; 2564 results.

23. MEDLINE; 18 [Limit to: English Language and Humans and (Age Groups All Adult 19 plus years)]; 11 results.

24. MEDLINE; 21 OR 22 OR 23 [Limit to: English Language and Humans and (Age Groups All Adult 19 plus years)]; 754 results.

4. MEDLINE; ((senile adj2 gout)).ti,ab; 4 results.

11. MEDLINE; 7 OR 8 OR 9 OR 10; 138145 results.

17. MEDLINE; CRITERIA/; 0 results.

10. MEDLINE; "classification criteria".ti,ab; 1926 results.

22. MEDLINE; 20 [Limit to: English Language and Humans and (Age Groups All Adult 19 plus years)]; 73 results.

25. AMED; "POLYMYALGIA RHEUMATICA".ti,ab; 11 results.

26. AMED; pmr.ti,ab; 73 results.

32. AMED; 28 OR 29; 51433 results.

33. AMED; 30 OR 31; 2820 results.

34. AMED; 27 AND 32; 20 results.

35. AMED; 27 AND 33; 0 results.

36. AMED; 34 OR 35; 20 results.

31. AMED; exp CLASSIFICATION/; 839 results.

27. AMED; 25 OR 26; 81 results.

37. AMED; 36 [Limit to: (Languages English)]; 18 results.

29. AMED; exp DIAGNOSIS/; 48040 results.

30. AMED; classification.ti,ab; 2498 results.

28. AMED; diagnosis.ti,ab; 7253 results.

40. CINAHL; (rheumatic AND gout).ti,ab; 34 results.

44. CINAHL; exp DIAGNOSIS/; 594031 results.

45. CINAHL; 43 OR 44; 629885 results.

46. CINAHL; classification.ti,ab; 16413 results.

39. CINAHL; exp POLYMYALGIA RHEUMATICA/; 211 results.

43. CINAHL; diagnosis.ti,ab; 77582 results.

49. CINAHL; 42 AND 45; 212 results.

50. CINAHL; 42 AND 48; 9 results.

51. CINAHL; 49 OR 50; 215 results.

52. CINAHL; 51 [Limit to: (Language English) and (Age Groups All Adult)]; 137 results.

48. CINAHL; 46 OR 47; 28330 results.

38. CINAHL; "polymyalgia rheumatica".ti,ab; 199 results.

41. CINAHL; PMR.ti,ab; 142 results.

42. CINAHL; 38 OR 39 OR 40 OR 41; 386 results.

47. CINAHL; exp CLASSIFICATION/; 14012 results.

53. EMBASE; exp RHEUMATIC POLYMYALGIA/; 3349 results.

58. EMBASE; 53 OR 54 OR 55 OR 56 OR 57; 5195 results.

67. EMBASE; 65 OR 66; 2213 results.

60. EMBASE; exp DIAGNOSIS/; 4038737 results.

66. EMBASE; 58 AND 64; 297 results.

57. EMBASE; (rheumatic adj2 gout).mp; 23 results.

65. EMBASE; 58 AND 61; 2087 results.

64. EMBASE; 62 OR 63; 1023293 results.

63. EMBASE; exp CLASSIFICATION/; 912220 results.

61. EMBASE; 59 OR 60; 4494654 results.

68. EMBASE; 67 [Limit to: Human and English Language and (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]; 882 results.

59. EMBASE; diagnosis.ti,ab; 1177342 results.

55. EMBASE; (polymyalgia adj2 rheumatic$).mp; 3710 results.

54. EMBASE; pmr.ti,ab; 2116 results.

62. EMBASE; classification.ti,ab; 205984 results.

56. EMBASE; (senile adj2 gout).mp; 3 results.

Appendix 2 Data extraction form and quality assessment criteria

Systematic Review Paper Assessment

Objective

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Method

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……

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Results

……

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Conclusion

……

……

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Other

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Quality Assessment

Criteria	
Clearly defined study objective	
Appropriate design for study question	
Inclusion and exclusion criteria clear and appropriate	
Representative sample (and comparison)	
Sample size calculation presented	
Appropriate selection of outcome	
Appropriate measurement of outcome	
Standardised collection of data	
Adequate length of follow up for research question	
Baseline participation >70% (all groups)	

Losses and drop outs <20%	
Adequate description of losses and completers	
Appropriate analysis of outcomes measured	
Numerical description of important outcomes given	
Adjusted and unadjusted calculations provided (with CI if appropriate)	
Total	

Diagnostic Indicator	Sens/Spec etc	Significance
1)		
2)		
3)		
4)		
5)		
6)		

Classification criteria Used if any:

1)
2)
3)
4)
5)
6)
7)

Appendix 3 Development of questions for the PMR questionnaire survey

Development of questions relating to diagnosis

Relevant theme derived from systematic review and other existing literature	Relevant area of UK PMR guideline	Process of stakeholder questionnaire review and refinement	Question in survey questionnaire
Classification criteria studies • Section 3.4.3	Section 1 (i) Core inclusion criteria • Age >50 years		Question 1 Age at which the diagnosis of PMR would be excluded?
Classification criteria studies • Section 3.4.3 Clinical features studies • Section 3.4.4	Section 1 (i) Core inclusion criteria • Bilateral shoulder or pelvic girdle aching • Morning stiffness • Evidence of an acute phase response		Question 2 Importance of key features
Classification criteria studies • Section 3.4.3 Laboratory investigations and unique biomarkers • Section 3.4.5	Section 1 (i) Core inclusion criteria • Evidence of an acute phase response Section 2 • Laboratory investigations before commencement of steroid therapy		Question 3 Use of inflammatory markers
Classification criteria studies • Section 3.4.3	Section 1 (i) Core inclusion criteria • "PMR can be diagnosed with normal inflammatory markers"		Question 4 Actions undertaken if inflammatory markers are normal
All sections relevant as studies identified to exclude other causes for symptoms and discriminate PMR from other mimicking disorders • Section 3.4.3 • Section 3.4.4 • Section 3.4.5 • Section 3.4.6	Section 1 (ii) Core Exclusion criteria • Active infection • Active cancer • Active GCA Other exclusions • Other inflammatory rheumatic diseases • Drug induced myalgia • Chronic pain syndromes		Question 5 Disorders routinely excluded before making a diagnosis

	• Endocrine disease • Neurological disease		
Laboratory investigations and unique biomarkers • Section 3.4.5	Section 2 • Laboratory investigations before commencement of steroid therapy		Question 7 Investigations routinely performed
All sections relevant as studies not able to definitively identify gold standard diagnostic criteria or tests • Section 3.4.3 • Section 3.4.4 • Section 3.4.5 • Section 3.4.6			Question 15 Challenges of PMR diagnosis

Development of questions relating to treatment

Relevant theme derived from systematic review and other existing literature	Relevant area of UK PMR guideline [Dasgupta 2010]	Process of stakeholder questionnaire review and refinement	Question in survey questionnaire
Helliwell et al 2013	Section 1 (iv) and Section 5 • Initial standardised dose 15mg		Question 6 Initial dose of prednisolone used
	Section 4 • Incomplete, poorly sustained or non-response to corticosteroids		Question 8. Action undertaken if response to treatment is poor
	Section 5 • Intramuscular methylprednisolone may be used in milder cases (i.m. depomedrone)		Question 9 Previous use of methylprednisolone
	Section 7 • Recommended vigilant monitoring		Question 10 Follow up of PMR patients
Helliwell et al 2013	Section 6 • Recommended bone protection		Question 11Additional interventions or medications offered
	Section 4 • Recommendations for early referral		Question 12 Indications for referral
	Section 8 • Recommendations for the management of relapse		Question 13 Management of relapse
OMERACT 12 Helliwell et al 2016			Question 14 Perceived Impact on patients' lives
Helliwell et al 2013			Question 16 Challenges of PMR treatment

Development of questions relating to GCA

Relevant theme derived from systematic review and other existing literature	Relevant area of UK GCA guideline [Dasgupta (GCA) 2010]	Process of stakeholder questionnaire review and refinement	Question in survey questionnaire
Rarity of the disorder [Barraclough et al 2008]		→	18) Have you ever managed a patient with GCA?
	Section 1 • Symptoms	→	19)What symptoms would lead you to suspect GCA
	Section 1 • Signs	→	20) What signs would lead you to suspect GCA?
	Section 1 • Recommended investigations Section 2 • Urgent referral for specialist evaluation Section 4a • Immediate initiation of high-dose glucocorticoid	→	21) Management and referral pathways for suspected GCA
	Section 2 • Urgent referral for specialist evaluation	→	22) Specialist to who suspected GCA patients are referred
	Section 4a • Immediate initiation of high-dose glucocorticoid	→	23) Initiating dose of prednisolone

Appendix 4 PMR National cross-sectional survey documents

23 January 2012

Dr Toby Helliwell
Arthritis UK Primary Care Centre
Primary Care Sciences
Keele University

Dear Toby

Re: 'The challenges of diagnosis and management of polymyalgia rheumatic in primary care: a GP survey'

Thank you for submitting your revised project for review.

I am pleased to inform you that your project has been approved by the Ethics Review Panel.

If the fieldwork goes beyond the date stated in your application (June 2012) you must notify the Ethical Review Panel via Michele Dawson.

If there are any other amendments to your study you must submit an 'application to amend study' form to Michele Dawson. This form is available from Michele (01782 733588) or via http://www.keele.ac.uk/researchsupport/researchethics/

If you have any queries, please do not hesitate to contact Michele Dawson in writing to m.dawson@uso.keele.ac.uk

Yours sincerely

pp **Dr Roger Beech**
Chair – Ethical Review Panel

CC RI Manager

PMR National Cross-sectional Survey Questionnaire

Thank you for taking a few moments of your time to fill in this questionnaire. If it is more convenient, a link to an online version of the questionnaire can be found (your **unique identifier** can be found on the back of this questionnaire, **password pmrstudy**).

www.keele.ac.uk/pmr/

The first section looks at the identification of PMR

1) At what **age** would you consider excluding a diagnosis of PMR?
(Please tick one box only)

<30… ☐ <40… ☐ <50… ☐ <60… ☐ <70… ☐ Other…….

2) Please circle how important the following features are to you in making the diagnosis of PMR **(1 being the least important and 5 being the most important)**
(please circle one number on each line only)

	Least Important				**Most important**
Arm pain	**1**	**2**	**3**	**4**	**5**
Muscle Pain	**1**	**2**	**3**	**4**	**5**
Morning stiffness	**1**	**2**	**3**	**4**	**5**
Neck Pain	**1**	**2**	**3**	**4**	**5**
Bilateral shoulder pain	**1**	**2**	**3**	**4**	**5**
Shoulder limitation	**1**	**2**	**3**	**4**	**5**
Hip Limitation	**1**	**2**	**3**	**4**	**5**
Raised inflammatory markers	**1**	**2**	**3**	**4**	**5**
Response to corticosteroids	**1**	**2**	**3**	**4**	**5**
Leg pain	**1**	**2**	**3**	**4**	**5**

Generalised joint pain	**1**	**2**	**3**	**4**	**5**
Hip girdle pain	**1**	**2**	**3**	**4**	**5**
Unilateral Shoulder pain	**1**	**2**	**3**	**4**	**5**
Joint Stiffness	**1**	**2**	**3**	**4**	**5**

Other (Please Specify)

.....

.....

3) Please indicate which inflammatory marker you routinely use and what you would consider to be **raised/positive** in order for you to consider PMR as a diagnosis**. (Please tick as many boxes that apply and give a figure for each that you would consider significant in PMR)**

	ESR……..... ☐	CRP……..... ☐
Raised/Positive value	..... mm/hr	..... mg/l

4) If the inflammatory markers were normal would you:-
(Please tick as many boxes as apply)

Exclude diagnosis of PMR.... ☐ Recheck blood test... ☐

Offer a trial of treatment……. ☐ Refer to specialist…. ☐

Other ☐ Please specify .....

5) Which of the following would you **routinely try to exclude** as part of diagnosing PMR**. (Please tick as many boxes that apply)**

Active infection……. ☐ Active cancer……. ☐

Active Giant Cell/Temporal Arteritis….	☐	Rheumatoid arthritis……..	☐
Osteoarthritis…….	☐	Pain syndromes…….	☐
Other rheumatological diseases……	☐	Drug induced myalgias…….	☐
Endocrine disorders…….	☐	Neurological disease……	☐

Other ☐ Please specify ….....…….....

6) What initial dose of prednisolone do you tend to prescribe if you decide to treat for PMR?

.....mg

Which (if any) investigations do you perform routinely in suspected PMR? (**please tick any of the relevant boxes that apply)**

Full blood count…..…….	☐	ESR/CRP…..…….	☐
Rheumatoid factor ……...	☐	Glucose ……..	☐
Antinuclear antibodies ..…….	☐	Urea & electrolytes …….	☐
Creatinine Kinase ……	☐	Liver Function Tests ...…….	☐
Thyroid function Tests ..…….	☐	Bone profile ……..……...	☐
Protein electrophoresis ..…….	☐	Bence Jones Protein ……..	☐
Anti CCP antibodies.……...	☐	Prostate specific antigen ..…..	☐
Chest X-Ray …….	☐	Ultrasound …….	☐
Other imaging ……..……	☐	Urinalysis ……..……	☐
None …….	☐		

Other ☐ Please specify …….....

The following section concerns the management of PMR

7) Typically patients with PMR respond well to prednisolone. If the response was poor what would be your next step? **(Please tick as many boxes that apply)**

Exclude diagnosis of PMR.....	☐	Continue on the same dose……..	☐
Increase the dose of steroid…….	☐	Check ESR……..	☐
Refer to specialist……	☐	Other.....	☐

If Other please specify.....

.....
.....

8) Have you ever used Intra-Muscular methylprednisolone (depomedrone) as a treatment for PMR?

Yes……..... ☐ No……..... ☐

If yes, please comment on how effective you thought this treatment was.

.....
.....

.....
.....

9) When do you normally follow up your patients with PMR in the first year after starting treatment? **(please circle all that apply)**

Weeks 1 2 3 4 5 6

Months 2 3 4 5 6 7 8 9 10 11 12

Other. (Please specify)……

……..……...

10) With a newly diagnosed patient with PMR what additional interventions do you offer routinely? **(Please tick any that you offer)**

Bone protection (eg Bisphosphonate)..	☐	Gastric protection…...……...	☐
Analgesics …….....	☐	Physiotherapy..……..	☐
Alternative therapies ...……...	☐	Referral to secondary care .…	☐
Joint injection ……...	☐	Information leaflet ...……	☐
Website information ..……..	☐	Support group ……..……...	☐
None ..……	☐	Non-steroidal anti-inflammatory	☐
Other ☐	Please specify	……...	

If you have ticked alternative therapies please indicate which alternative therapies that you suggest.

.....
.....

…….....
.....

11) In what circumstances would you refer a patient with PMR to a specialist or secondary care? **(Please indicate all responses that are relevant to you)**

Routine (every patient)..……..……	☐	Never……..……...	☐
Confirm diagnosis.…….....	☐	Uncertain diagnosis……..	☐
High steroid requirements..…….	☐	Poor response……...…	☐
Medication complications……..	☐	Flare-up/relapse…...……	☐
Patient request……..……..	☐	Normal ESR……...……...	☐
Young patient……	☐	Please specify age cut-off…….	
Other……	☐	Please specify…….	

This section relates to relapse of PMR symptoms, living with PMR and problems that you or your patients may have experienced.

12) How would you manage a relapse in symptoms?
(Please tick what you feel are the most appropriate boxes)

Increase steroid until symptoms controlled..…….....	☐	Re-check inflammatory markers ……..….....	☐
Increase steroid dose only if ESR raised…….....	☐	Increase steroid by 5mg……..	☐
Increase steroid dose even if ESR was normal…….....	☐	Refer patient to secondary care……...	☐
Increase steroid to previous effective dose ……...	☐	Other.....	☐

If Other please specify.....

.....
.....

.....
.....

13) Thinking about patients that you have seen with PMR, how would you rate the **importance** to your patients of the following factors?
(Please circle one number on each line only)

	Least Important				**Most important**
Pain	**1**	**2**	**3**	**4**	**5**
Stiffness	**1**	**2**	**3**	**4**	**5**
Limitation of activity	**1**	**2**	**3**	**4**	**5**
Sleep	**1**	**2**	**3**	**4**	**5**
Mood	**1**	**2**	**3**	**4**	**5**
Intimate relationship issues	**1**	**2**	**3**	**4**	**5**
Medications	**1**	**2**	**3**	**4**	**5**
Side effects/Complications	**1**	**2**	**3**	**4**	**5**
Relapse	**1**	**2**	**3**	**4**	**5**
Worries about diagnosis	**1**	**2**	**3**	**4**	**5**

Other (Please specify)
.....

.....

14) Thinking about patients with PMR that you have seen before what challenges regarding their **diagnosis** did you encounter?

.....
.....

.....

.....

15) Thinking about patients with PMR that you have seen before, what challenges regarding their **treatment** did you encounter?

.....
.....

.....

.....

16) Generally, what **challenges** (if any) do you believe PMR poses to general practice?

.....
.....

.....
.....

Giant cell (GCA) or temporal arteritis (TA) is a common association with PMR. The following section relates to GCA

17) Have you ever managed a patient with GCA?

Yes……..... ☐ No……..... ☐

18) What **symptoms** would lead you to suspect GCA?
.....
.....

.....
.....

19) What **signs** would lead you to suspect GCA?
.....
.....

.....
.....

20) Considering the management of GCA, would you…
(Please tick one of the following)

Refer to hospital **immediately** as an emergency without investigation?..... ☐

Do urgent blood tests and refer to hospital **immediately** if elevated?……..... ☐

Do urgent bloods, initiate steroids and refer for outpatient specialist review **urgently** if bloods positive? ☐

Do urgent bloods, initiate steroids and refer for outpatient specialist review **routinely**?..……..... ☐

Other ☐ Please specify ……..…….....

21) Who would you routinely refer to?

(Please tick the 1 box that is most relevant to you)

A&E……. ☐ Elderly care…… ☐

Rheumatology…… ☐ Opthamology……. ☐

General medicine…….. ☐ Neurology……... ☐

Other ☐ Please specify ……..…….....

22) If you were to initiate prednisolone what initial dose would you prescribe?

.....mg

The following section asks a few questions about you and your practice.

Age ……....years

Gender: Female…….... ☐ Male…….... ☐

Current role Salaried....☐ Locum....☐ Partner....☐ Senior partner....☐

What year did you qualify as a doctor? …….....

What year did you qualify as a GP? ……..…..

How many patients do you have on your practice list? ……

Are there any resources or guidelines that you refer to, to help you manage patients with PMR or GCA

Yes……..... ☐ No……..... ☐

(Please specify).....
.....

.....
.....

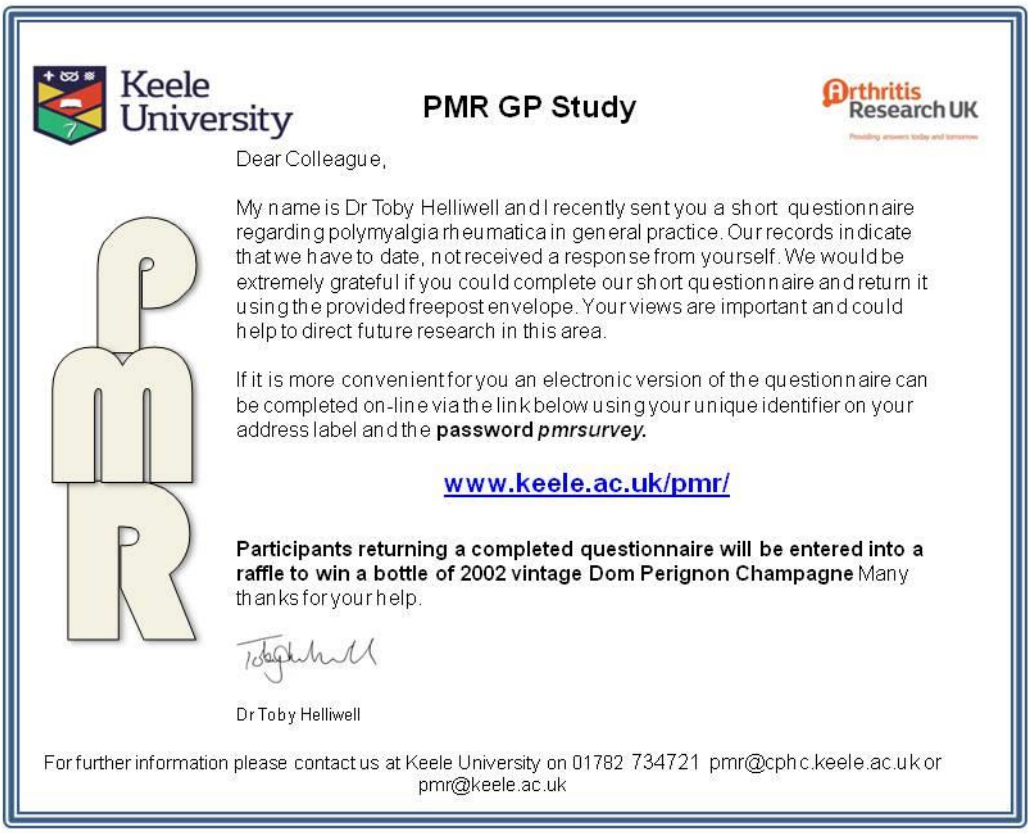
Would you be happy to be contacted in the future to discuss PMR in more depth?

Yes……..... ☐ No……..... ☐

Thank you for taking the time to fill in this questionnaire and help with this important research.

Address label

PMR National Cross-sectional Survey: Reminder Card



Keele University

PMR GP Study

Arthritis Research UK

Dear Colleague,

My name is Dr Toby Helliwell and I recently sent you a short questionnaire regarding polymyalgia rheumatica in general practice. Our records indicate that we have to date, not received a response from yourself. We would be extremely grateful if you could complete our short questionnaire and return it using the provided freepost envelope. Your views are important and could help to direct future research in this area.

If it is more convenient for you an electronic version of the questionnaire can be completed on-line via the link below using your unique identifier on your address label and the **password** ***pmrsurvey.***

www.keele.ac.uk/pmr/

Participants returning a completed questionnaire will be entered into a raffle to win a bottle of 2002 vintage Dom Perignon Champagne Many thanks for your help.

Dr Toby Helliwell

For further information please contact us at Keele University on 01782 734721 pmr@cphc.keele.ac.uk or pmr@keele.ac.uk

PMR National Cross-sectional Survey: covering letter

PRIMARY CARE SCIENCES
ARTHRITIS RESEARCH UK PRIMARY CARE CENTRE

PMR GP Survey

Dear Colleague,

My name is Dr Toby Helliwell and I am a GP working at Keele University and also in practice in Newcastle-Under-Lyme, North Staffordshire. As part of my GP training I undertook a small project looking at the management of polymyalgia rheumatica (PMR) in general practice. PMR is the commonest inflammatory rheumatological disorder of the elderly and on average a full-time GP will see 4 to 5 cases of PMR per year. Work done by Dr Kevin Barraclough, a GP based in Gloucestershire, showed that over 80% of patients with PMR are managed solely by their GP. Despite this the majority of PMR research has been conducted in secondary care, where the patients may be different from those we manage in primary care.

Diagnosing and managing PMR in primary care can sometimes be challenging. To try to better understand this, we have developed a short questionnaire, which we would be very grateful if you could complete. As a GP I know that we are asked to fill in many questionnaires, and, that time is precious, but it should only take a few minutes of your time to complete and a pre-paid return envelope is included. Your views are important and could help to direct future research in this area. If you feel it would be more convenient for you the questionnaire can be completed on-line via the link below using the unique identifier on your address label and the link (password ***pmrsurvey***):

www.keele.ac.uk/pmr/

Participants returning a completed questionnaire will be entered into a prize draw to win a bottle of 2002 vintage Dom Perignon Champagne. We hope our findings will go on to help develop primary care orientated guidance and management strategies and so improve outcomes for this common disorder.

Thank you for your help.

Dr Toby Helliwell MRCGP
GP research Fellow

Label 10

Appendix 5 Development of topic guide used for the qualitative telephone interview study

Systematic review and guidelines used to develop questionnaire

PMR Diagnosis literature	BSR/BHPR PMR guidelines [Dasgupta et al 2010]
Classification criteria studies, Section 3.4.3	Section 1 (i) Core inclusion criteria Age >50 years
Classification criteria studies, Section 3.4.3 Clinical features studies, Section 3.4.4	Section 1 (i) Core inclusion criteria
Classification criteria studies, Section 3.4.3 Laboratory investigations and unique biomarkers, Section 3.4.5	Section 1 (i) Core inclusion criteria, Evidence of an acute phase response Section 2, Laboratory investigations before commencement of steroid therapy
Classification criteria studies, Section 3.4.3	Section 1 (i) Core inclusion criteria "normal inflammatory markers"
Exclude other causes for symptoms Section 3.4.3, Section 3.4.4, Section 3.4.5, Section 3.4.6	Section 1 (ii) Core Exclusion criteria Other causes for symptoms
Laboratory investigations and unique biomarkers, Section 3.4.5	Section 2 Laboratory investigations before commencement of steroid therapy
All sections relevant as studies not able to definitively identify gold standard diagnostic criteria or tests Section 3.4.3, Section 3.4.4, Section 3.4.5, Section 3.4.6	

PMR Management literature	BSR/BHPR PMR guidelines [Dasgupta et al 2010]
Helliwell et al 2013	Section 1 (iv) and Section 5 Initial standardised dose 15mg
	Section 4. Incomplete, poorly sustained or non-response to corticosteroids
	Section 5.Intramuscular methylprednisolone may be used in milder cases (i.m. depomedrone)
	Section 7. Recommended vigilant monitoring
Helliwell et al 2013	Section 6. Recommended bone protection
	Section 4. Recommendations for early referral
	Section 8. Recommendations for the management of relapse
OMERACT 12 [Helliwell et al 2016]	Life Impact

BSR/BHPRGCA guidelines [Dasgupta (GCA) et al 2010]
Section 1, GCA Symptoms
Section 1, GCA Signs
Section 1, Recommended investigations Section 2, Urgent referral for specialist evaluation Section 4a, Immediate initiation of high-dose glucocorticoid
Section 2, Urgent referral for specialist evaluation
Section 4a, Immediate initiation of high-dose glucocorticosteroid

Findings of questionnaire survey

- Features used by GPs for PMR identification Section 5.3
- Importance of excluding mimicking disorders Section 5.3.3
- Advised Investigations not routinely performed Sections 5.3.2.1, 5.3.2.2
- Challenges: Atypia Diagnostic uncertainty Mimicking disorders Multimorbidity Section 5.3.6
- Challenges: Dose reduction Adverse effects Treatment duration Section 5.4.3
- Initial prednisolone dose Section 5.4.1
- Management of relapse/flares Section 5.4.2.2
- Specialist referral Diagnostic uncertainty Atypia Section 5.4.2.2
- Adjuvant treatment Section 5.4.2.1
- GCA Management Initiating dose Referral Challenges Section 7.5.3
- GCA symptoms and signs Section7.5.1

Topic guide questions

Diagnosis
"How would you diagnose PMR?"
Expand/probe/challenge, typical symptoms for you, normal inflammatory markers, young patients, response to treatment, role of blood tests or investigations, multimorbidity, challenges experienced

Challenges
"What other general challenges do disorders like PMR pose in general practice?"
Expand/probe/challenge, overall role of GP, fears, thoughts on how to improve, what would be the ideal, how could that be achieved, barriers encountered

Management
"How do you treat PMR?"
Expand/probe/challenge, initial dose, response to treatment, do you offer any other treatment, prophylaxis, manage relapse, challenges experienced referral

GCA
"What features would make you think of GCA?"
"How do you treat GCA?"
Expand steroid dose, investigations, referral, what features would worry you

Appendix 6 Qualitative study investigating the diagnostic and management challenges of PMR and GCA in primary care documents

A qualitative study investigating the diagnostic and management challenges of PMR in primary care: Topic guide

Polymyalgia Rheumatica: A qualitative Investigation
Topic Guide

Aim: To explore in-depth the views of general practitioners towards the diagnosis and management of polymyalgia rheumatic in primary care and to identify perceived barriers to effective diagnosis and management

Introduction

- Introduce myself and the study aims, introduce interview (length, tape recording)
- Discuss reimbursement
- Explain voluntary nature of participation, right to withdraw & confidentiality
- Ask if participant has any questions

Background and initial open PMR questions

- Discuss current job, practice, seniority, interests
- "Tell me about your professional experiences with PMR"
  "Tell me about the last case of PMR that you saw"

Keep brief

Diagnosis

- "How would you diagnose PMR in your day to day practice"
  Expand/probe/challenge,
    - Typical symptoms for you
    - normal inflammatory markers
    - young patients
    - response to treatment
    - role of blood tests or investigations
    - multimorbidity
    - challenges experienced

Management

- "How do you treat PMR"
  Expand/probe/challenge,
    - Initial dose
    - How important is response to treatment
    - Do you offer any other treatment

- Do you offer prophylaxis
- How do you manage relapse
- Challenges experienced
- Referral

Challenges

- "We have talked about several challenges with regards to diagnosis and management of PMR by GPs, what other general challenges do disorders like PMR, that aren't often encountered pose in general practice"

  Expand/probe/challenge
  - Overall role of GP
  - Fears
  - Thoughts on how to improve
  - What would be the ideal
  - How could that be achieved
  - Barriers encountered

GCA

Dependent on time available and if brought up by interviewee

- What features would make you think of GCA
- How do you treat GCA
  - Expand steroid dose, investigations, referral
- What features would worry you

Summary

- Any other thoughts that you would like to discuss or share
- Re-check consent
- Thank participant for their time
- Any questions for me

A qualitative study investigating the diagnostic and management challenges of PMR in primary care: reply slip

Version 1.0 10/10/13 Researchers: T Helliwell, S Muller, J Richardson, S Hider, C Mallen

Reply slip for research study-
PMR in general practice: A qualitative study

Yes, I would like to take part in the study ☐

No, I do not wish to take part in the study ☐

Name:……..

Address:……..

……..

……..

……..

Contact number:……

Email:……..

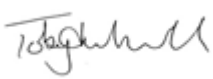
Preferred contact method to arrange a suitable time for interview:

Telephone ☐

Email ☐

Please return the form in the pre-paid envelope provided.

Thank you for your help with this research study



Dr Toby Helliwell

A qualitative study investigating the diagnostic and management challenges of PMR in primary care: consent form

Version 1.0 10/10/13 Researchers: T Helliwell, S Muller, J Richardson, S Hider, C Mallen

CONSENT FOR TAKING PART IN THE STUDY

PMR in general practice: A qualitative study

1. I confirm that I have read and understand the information sheet and have had the opportunity to ask questions…… ☐
2. I understand that my participation is voluntary, that I can refuse to answer a question or withdraw my consent at any time, without giving reason and without my professional role being compromised…… ☐
3. I understand that the interview will be recorded and transcribed verbatim and that recording will be stored in a secure location, but will bear no identifying information. I also understand that the recordings may be kept for up to 20 years and after this time they will be destroyed…… ☐
4. I understand that, should I lose the capacity to consent to be in the study, the research centre would retain any information collected prior to this point, but would not involve me in any further part of the study…… ☐
5. I understand that the data collected during the study may be looked at by individuals from Primary Care Sciences, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission to these individuals to have access to my records… ☐
6. I understand that quotations from the interview may be included in reports or publications from this study, but that these will be anonymous and I will not be identifiable……..... ☐

   I **DO** want to see all quotations obtained during my interview before publication…… ☐

   I **DO NOT** want to see the quotations obtained during this interview before publication…… ☐

7. I agree to take part in the study…… ☐

Please sign and date:

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of researcher	Date	Signature

Thank you for your help with this research project

For any further information about this study, please telephone: Dr Toby Helliwell (01782 734895)

A qualitative study investigating the diagnostic and management challenges of PMR in primary care: covering letter

Version 1.0 10/10/13 Researchers: T Helliwell, S Muller, J Richardson, S Hider, C Mallen

PMR in general practice: A qualitative study

Participant information leaflet

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disorder seen in older patients. The majority of patients with the disorder are identified, diagnosed and managed exclusively by general practitioners yet the majority of research to date has focused on secondary care. As such little is known about the management and diagnostic challenges that PMR poses in primary care.
This leaflet explains what will happen if you decide to take part in the study. If there is anything that is not clear, or you require further information, please contact the research team:

Mondays and Thursdays: Dr Toby Helliwell 01782 734829
Tuesdays, Wednesdays, Fridays
Alternatively, email t.helliwell@keele.ac.uk

What is the purpose of the study?
This study aims to explore in depth the beliefs, challenges and experiences of GPs on the management and diagnosis of PMR in the community. We are particularly interested in your views on what typical features you use to diagnose PMR and any diagnostic or management challenges that you have faced. This is particularly pertinent for general practitioners as they are often the first clinicians approached by patients and, as no commonly agreed diagnostic criteria nor gold standard test exists for PMR, diagnosis can be difficult. GPs too, are often intimately involved in the on-going management and monitoring of the majority of PMR patients. This remains an area where there has historically been little research focus. Your opinions will help direct further research initiatives and identify areas where GPs could be better supported in diagnosing and managing PMR.

Do I have to take part?
We are writing to you because, when you completed a questionnaire as part of the 'PMR National GP survey' study, you agreed to further contact. We would like to carry out some follow-up research to explore some of the issues raised in more detail and wondered if you could help again. ***You are, of course, entirely free to choose whether or not to take part***. If you decide to take part, you will be asked to sign a consent form entitled 'consent for taking part in the study and use of quotes'. After giving consent, you are still free to withdraw at any time without giving reason. Your decision to take part in the study, or to withdraw, will not affect any legal rights. If you would like to take part, please return the enclosed reply slip and consent form and we will contact you.

What will happen to me if I agree to take part?
If you agree to take part, you will be contacted by telephone to arrange a subsequent telephone interview, at a time most convenient for you. The interview will last approximately 20-30 minutes and it will focus on your experiences on diagnosis and management of PMR. Since we are interested in your opinions, there are no right or wrong answers. No preparation for the interview is necessary and this is not a test about your knowledge. We would like to record the interview and will check that this is acceptable to you prior to the interview. The interview will then be transcribed into text. Both the recording and the text will be stored in a secure location, only accessed by the research team. Both the recording and the text will contain no personal identifiable information. We will ask if you would like a copy of the transcribed interview for your records. We will store the recordings securely for 20 years, after which they will be destroyed.

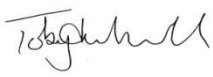
During the interview, you can choose not to answer questions, or to end the interview at any time. You will be asked at the end of the interview if you are still happy to be included in the study. If you decide that you would like to withdraw your consent, your interview will not be used. In order to convey the attitudes and beliefs of participants, we would like to use direct quotations from the interview. On the consent form we have included a section specifically for the use of direct quotations. We would be grateful if you could complete this section also, however if you do not wish quotes to be used please check the relevant box. You will be asked at the end of the interview again if you would still be willing to allow quotes to be used if you had agreed on the initial consent form.

Any information you give in the interview will not be passed on to anyone else without your permission. If your interview contains comments that might identify a third party (e.g. GP, surgery, hospital), we will ensure that the person or institution cannot be identified in any account or published report of this study.

What are the possible benefits and risks of taking part?
There are no direct risks relating to medical treatment in this study, neither are there any intended direct medical benefits. There may be an indirect benefit to patients from the insights we gain, but of course, we cannot guarantee this.
Occasionally during interviews like these, some people may feel some distress, perhaps a topic may prompt unhappy memories or distressing thoughts. If this happens and you do not wish to discuss this further, the topic will not be followed up again during the interview. The study is not intended to be of any educational benefit.

Who is organising and funding the research, and is it ethical?
This study is part of a programme of work being conducted by the Arthritis Research Campaign National Primary Care Centre at Keele University. It is
funded by the National Society of Primary Care Research and ethical approval has been obtained from the Keele University Ethical Review Panel.

Thank you for your time



Dr Toby Helliwell

Appendix 7 **HELLIWELL, T., HIDER, S.L., BARRACLOUGH, K., DASGUPTA, B. and MALLEN, C.D., 2012. Diagnosis and management of polymyalgia rheumatica. *The British journal of general practice : the journal of the Royal College of General Practitioners,* 62(598), pp. 275-276.**

BARRACLOUGH, K., MALLEN, C.D., HELLIWELL, T., HIDER, S.L. and DASGUPTA, B., 2012. Diagnosis and management of giant cell arteritis. *The British journal of general practice : the journal of the Royal College of General Practitioners,*62(599), pp. 329-330.

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Diagnosis and management of polymyalgia rheumatica

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Kevin Barraclough, MA, FRCP, MRCGP, AFOM, LLB, GP, Painswick Surgery
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Christian D Mallen, MMedSCi, MPhil, PhD, MRCGP, professor of general practice, director of academic general practice, director of clinical academic training, Arthritis Research UK clinician scientist, GP

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See "Diagnosis and management of polymyalgia rheumatica" in volume 62 on page 348.

See "Integrated approach to prescribing education" in volume 62 on page 350.

This article has been cited by other articles in PMC.

INTRODUCTION

Polymyalgia rheumatica (PMR) is the commonest inflammatory rheumatic disorder affecting older people.[1]Patients typically present with bilateral shoulder pain, morning stiffness, raised inflammatory markers, and have a rapid response to low-dose corticosteroids. There is no gold standard diagnostic test and despite being first described in 1888, controversies still exist as to its defining characteristics. PMR carries a lifetime risk of 2.4% for females and 1.7% for males.[2] The incidence in the UK has been shown to be 8.42 per 10 000 person years.[3] In the UK, the majority of patients are managed exclusively in primary care[4] with an average full-time GP seeing five new cases of PMR per year.[5] Accurate diagnosis can be challenging even for specialists, but is essential as many serious illnesses can mimic PMR. Guidelines for the diagnosis and management of PMR have recently been published by the British Society of Rheumatologists (BSR) and British Health Professionals in Rheumatology (BHPR).[6]

DIAGNOSIS

Consider PMR in patients over the age of 50 years with:

- ≥2 weeks of bilateral shoulder and/or pelvic girdle ache;
- morning stiffness; and
- raised inflammatory markers.

Subsequent clinical assessment and investigations should be directed towards excluding disorders that can mimic PMR (Box 1). Suggested initial investigations include full blood count, renal, thyroid, and liver function, inflammatory markers (erythrocyte sedimentation rate [ESR]/C-reactive protein [CRP]), bone, protein electrophoresis, rheumatoid factor, urinary Bence Jones protein, creatinine kinase, and dipstick urinalysis. Additional investigations if clinically appropriate include antinuclear antibodies, anti-cyclic citrullinated peptide antibodies, and chest X-ray. Ultrasound of the shoulders and/or hips may show characteristic lesions such as sub-deltoid bursitis, bicipital tenosynovitis, and joint fluid.[7]

Box 1. Disorders that can mimic polymyalgia rheumatica

Rheumatological disorders

Inflammatory

- Late-onset rheumatoid arthritis, spondylo-arthritides, psoriatic arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis, inflammatory myopathies

Non-inflammatory

- Osteoarthritis, rotator cuff disorders, frozen shoulder

Infection

- Tuberculosis, bacterial endocarditis, osteomyelitis, septic arthritis, other infections, for example, urinary tract infections

Malignancies

- Lymphoma, myeloma, and leukaemia. Solid tumours, and metastases, for example, prostate, bowel, lung, breast, and renal

Other

- Endocrine disorders (for example, hypo/hyperthyroidism, hyper/hypoparathyroidism)
- Drug induced myalgia (for example, statins)
- Parkinson's disease

Giant cell arteritis (GCA) is a serious association of PMR. The latest guidance is summarised in an associated article.[8]

TREATMENT

A rapid response to low dose prednisolone (15 mg) is typical. However, a poor response should prompt further assessment for an alternative diagnosis or consideration for a specialist review. Patients taking long-term corticosteroids are at high risk of developing osteoporosis. Current guidance suggests offering osteoporosis prophylaxis (bisphosphonate and calcium/vitamin D supplementation) to those who are at high risk of fracture (≥65 years or prior fragility fracture).[6] In other individuals calcium/ vitamin D supplementation and a dual-emission X-ray absorptiometry scan is recommended.[6] Although not part of this latest guidance, gastric symptoms, are commonly reported among patients with PMR.[9] Gastric protection should therefore be strongly considered especially in at-risk patients.

ONGOING MANAGEMENT

Robust clinical evidence for corticosteroid tapering is lacking. An initial dose of 15 mg of prednisolone coupled with a slow reduction in dose is effective at maintaining remission.[10] Guidance suggests 15 mg of prednisolone for 3 weeks, followed by 12.5 mg for 3 weeks, then 10 mg for 4–6 weeks, and finally a reduction in dose of 1 mg every 4–8 weeks. After initial diagnosis, follow-up to assess response within 1 week is suggested. Subsequently a review of symptoms, progress, adverse side effects, complications of treatment, atypical features, and an assessment for GCA is suggested in weeks 3 and 6 and again, 3, 6, 9, and 12 months after diagnosis. This treatment and follow-up regimen serves only as a guide and should be modified according to individual patients' response and ongoing progress. Relapses should be assessed by clinical symptoms rather than being guided by laboratory results (such as ESR and CRP). Management of relapse should involve an increase of prednisolone to the previously higher dose that controlled symptoms, followed by reassessment.[6] Recurrent relapses (more than two) are an indication for specialist referral for consideration of steroid sparing agents such as methotrexate.

PATIENT EDUCATION AND SELF-MANAGEMENT

All patients should be provided with written information on PMR and corticosteroid treatments. They should also be given information on range-of-motion exercises for the shoulder and provided with contacts to their local Polymyalgia Rheumatica & Giant Cell Arteritis UK patient support group.[11]

REFERRAL

A wide range of illnesses can mimic PMR, some of which respond to corticosteroid therapy. Accurate diagnosis is therefore essential, ongoing management can usually continue in primary care once diagnosis has been confirmed. In cases of diagnostic uncertainty early referral for specialist review is essential. Some examples of indications for early referral are summarised in Box 2.

Box 2. Indications for early referral to specialist

Atypical features

- Age <60 years
- Chronic onset
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- Red flag features (prominent systemic features, weight loss, night pain, neurological signs)
- Features of peripheral arthritis, muscle disease, and other autoimmune/systemic diseases
- Very high or normal inflammatory markers

Treatment dilemmas

- Poor/incomplete response to corticosteroids
- Inability to reduce corticosteroid therapy
- Recurrent relapse
- Contraindications to corticosteroid therapy
- Prolonged treatment duration (>2 years)

CONCLUSION

PMR is a commonly-seen disorder that is often managed exclusively in primary care. The BSR/BHPR guidance brings together the best evidence and extensive expert opinion to provide a much needed safe approach to the identification and ongoing management of this common inflammatory rheumatological disorder. Accurate diagnosis is key. Further early expert review should be sought in situations where diagnosis is uncertain. The guidance reinforces a more holistic approach to PMR emphasising the need to consider the prevention and management of potential side effects and complications of treatment. Dissemination of this guidance to general practice, where the majority of patients are managed, will hopefully facilitate accurate diagnosis and improve the ongoing management and, therefore, outcomes for patients with PMR.

Notes

Provenance

Freely submitted; not externally peer reviewed.

Discuss this article

Contribute and read comments about this article on the Discussion Forum: http://www.rcgp.org.uk/bjgp-discuss

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Diagnosis and management of giant cell arteritis

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INTRODUCTION

Giant cell arteritis (GCA) is the commonest form of large-vessel vasculitis and affects branches of the external carotid artery but also the ciliary and retinal arteries. The symptoms are caused by local ischaemia due to endovascular damage and cytokine-mediated systemic illness. There is considerable overlap with polymyalgia rheumatica (PMR): 16–21% of patients with PMR have GCA on temporal artery biopsy, and symptoms of PMR are present in 40–60% of patients with GCA.[1] GCA occurs in 2.2 per 10 000 patient-years in the UK.[2] A full-time GP may expect to see one new case every 1–2 years. It is virtually unknown in people aged under 50 years. Early recognition is critical to prevent visual loss, that otherwise occurs in up to 20% of cases.[3] Once high-dose corticosteroids are started, visual loss is extremely rare.

Guidelines for the diagnosis and management of GCA, have recently been published by the British Society of Rheumatologists and British Health Professionals in Rheumatology.[4]

DIAGNOSIS

A 2002 systematic review analysed the presenting clinical features in a mixture of studies, with a total of 1435 cases of giant cell arteritis.[5] The mean duration of symptoms at diagnosis was 3.5 months.[5] The results in Table 1 demonstrate the somewhat protean manifestations of this condition.

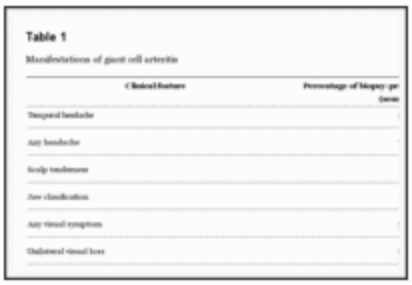

Table 1
Manifestations of giant cell arteritis

The sensitivity of individual clinical features was relatively low: 24% of cases had no headache at all, and only 52% had a temporal headache. The diagnosis is easily missed when systemic symptoms (such as low-grade fever or weight loss), ischaemic symptoms (jaw claudication or transient visual symptoms), or polymyalgic symptoms (proximal myalgia or morning stiffness) predominate over the well-known hallmark of temporal headache. Unfortunately, there is some evidence that this subgroup (without headache as the dominant symptom) may be at increased risk of visual loss. A recent audit of 65 patients with GCA showed that 44 had had unrecognised visual disturbance, visual loss, or stroke in the mean of 35 days between onset of symptoms and diagnosis (range 2–336 days).[6] Eleven of these patients presented without headache or scalp tenderness, and 10 of these had visual loss.

Only 4% of patients with GCA have a completely ‘normal’ erythrocyte sedimentation rate (ESR) but nearly one-fifth have an ESR >50 mm/hour.

There is some evidence that GCA may be underdiagnosed. A 1971 Swedish study examined 1097 consecutive autopsies, with temporal artery examination carried out in each of them. Sixteen cases of undiagnosed GCA were identified (1.5% of the study population). Retrospective analysis of the case notes documented typical features of undiagnosed GCA in nine.[7]

Localities need to have a clear pathway for suspected GCA because GPs are often uncertain whether to refer to rheumatologists, ophthalmologists, or vascular surgeons.

Temporal artery ultrasound may become more used in diagnosis. A meta-analysis of studies of temporal artery ultrasound against a gold standard of temporal artery biopsy found a sensitivity of 69% and a specificity of 82%.[8]

BIOPSY

Urgent referral for specialist assessment and temporal artery biopsy is suggested for all patients with suspected GCA, although this should not delay initiation of immediate corticosteroid treatment. The biopsy can retain the characteristic giant cell histology for 2–6 weeks after initiation of treatment but should ideally be done within 2 weeks. The biopsy may be negative in 13% of true cases (possibly because of ‘skip lesions’).[9] If the clinical features are typical, the patients should, nevertheless, be treated.

TREATMENT

High-dose glucocorticosteroid therapy should be initiated immediately the diagnosis is suspected. There are few risks in starting treatment erroneously (the treatment can always be stopped) and delayed treatment can result in sudden visual loss. In the absence of ischaemic symptoms (jaw claudication or visual symptoms), it is reasonable to start on 40 mg prednisolone daily orally. If the patient has jaw claudication, the risk of visual loss is high and 60 mg prednisolone should be used. If the patient already has visual symptoms of any sort, then immediate admission for 3 days of intravenous methylprednisolone is necessary to preserve vision.

The initial dose of oral prednisolone is maintained until symptoms have resolved and inflammatory mediators have normalised. The dose can then be reduced by 10 mg at 2-week intervals until the patient is taking 20 mg daily, and then reduced by 2.5 mg steps each 2 weeks to 10 mg. Thereafter, a reduction of 1 mg per month every 4–8 weeks is recommended, as with PMR. Most patients have stopped treatment by 2 years. Review with measured inflammatory markers is initially weekly, tapering to monthly, and then 3-monthly.

Low-dose aspirin should be considered in those patients without contraindications and bisphosphonates with calcium and vitamin D supplementation are recommended for all patients on long-term corticosteroids.

Relapse is usually, but not always, associated with a rise in inflammatory markers. Rarely, patients may develop a more widespread vasculitis of the aortic arch and its branches. Upper-limb claudication, absent pulses, or widening of the mediastinum on a chest X-ray should prompt urgent specialist evaluation.

PATIENT EDUCATION AND SELF-MANAGEMENT

Patients should receive written information on GCA (such as the Arthritis Research Campaign booklet on GCA), together with instructions about seeking urgent review in the event of any return of symptoms. Support can be obtained from the local Polymalgia Rheumatica and Giant Cell Arteritis UK (PMRGCAUK) patient support group (http://www.pmrgcauk.com/).

CONCLUSION

GCA is the commonest form of vasculitis. A GP will encounter a new case roughly once every 1–2 years. Early recognition and treatment with high-dose corticosteroids is crucial to preventing the visual loss that occurs in 20% of patients. There is evidence that the risk of visual loss is higher in patients with jaw claudication and in patients who do not have the typical temporal headache. The starting dose for prednisolone is 40 mg to 60 mg. Specialist referral is advised and temporal artery biopsy should ideally occur within 2 weeks.

Notes

Provenance

Freely submitted; not externally peer reviewed.

Discuss this article

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Appendix 8 MALLEN, C., HELLIWELL, T., O'BRIEN, A., MACKIE S., 2014. Polymyalgia rheumatica. ARUK reports on the Rheumatic Diseases, Series 7, Spring 2014. Hands On No 4

Polymyalgia rheumatica

1. Editorial
2. Introduction
3. Making the diagnosis
4. How to treat and monitor PMR
5. Do not miss giant cell arteritis
6. Specialist referral
7. Key messages
8. Continuing professional development (CPD) tasks
9. References
10. Further reading and useful resources
11. Patient resources

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[1] Arthritis Research UK Primary Care Centre, Keele University
[2] School of Health and Rehabilitation, Keele University
[3] Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital

Download Issue 4 (Hands On Series 7) Spring 2014

Editorial

Polymyalgia rheumatica (PMR) is a condition that is commonly seen in older patients in primary care. It is known that there is wide variation in clinical practice with respect to diagnosis and management. The challenges include having no gold standard test for it, the possibility of atypical presentation and the existence of other conditions that can mimic it.

Having made the diagnosis it is important to balance treatment efficacy against potential side-effects. Patients vary in their response to steroids and the rate at which their treatment can be tapered.

Patients with PMR are likely to already have co-morbidities or to be at risk of developing them due to steroid treatment. Primary care has a key role in screening and monitoring for hypertension, diabetes and bone health. Again it is known that there is often room for improvement here.

The authors of this report address these challenges with a very practical and useful guide to how assessment and management can be improved. This is definitely something to keep to hand as you see patients with PMR.

Simon Somerville, Medical Editor

Introduction

Polymyalgia rheumatica (PMR) is the commonest inflammatory rheumatological disorder of older people, with an incidence of 8.4/10,000 person-years (95% CI 8.3 to 8.6) and a lifetime risk of 2.4% for women and 1.7% for men.[1,2] It is characterised by bilateral pain and stiffness of the hips and shoulders and is often associated with profound disability. The majority of patients with PMR are exclusively managed in the community, yet diagnosis can be difficult, especially for those with an atypical presentation. A recent analysis of GP consultation databases suggests that current primary care management may be suboptimal and that patient care could be improved.[3] The aim of this edition of Hands On is to provide an evidence-based overview to the successful diagnosis and management of patients with PMR in general practice settings.

Making the diagnosis

PMR is uncommon in those under 60 years. For many patients, the onset of PMR is abrupt and may start with fevers or chills ('the flu that does not go away'). Patients complain of pain in the shoulders and

hips that is associated with stiffness, especially in the morning. They often report that they rapidly deteriorate over a period of 1–2 weeks, becoming so disabled that they are no longer able to get off the toilet without help or turn over in bed. Patients usually have elevated inflammatory markers (e.g. ESR, CRP or where available plasma viscosity, PV) and may report systemic features such as malaise and fatigue. Treatment with low-dose glucocorticoids (e.g. prednisolone) produces a dramatic response in around 80–90% of patients.

The lack of a 'gold standard' (100% specific) diagnostic test makes diagnosing PMR challenging even for experts.[4] As such a thorough and systematic diagnostic work up is essential in primary care to exclude other conditions that commonly present with a polymyalgic syndrome. These commonly include both rheumatological and non-rheumatological disorders, some of which may initially improve with glucocorticoid treatment, and so response to treatment is not diagnostic of PMR.[4] Therefore patients who do not have a rapid, complete response (see below for definition) warrant re-consideration of the diagnosis.

A number of 'core' investigations are recommended by the British Society for Rheumatology.[5] These are intended to help guide the diagnostic process and are presented in Box 1.

BOX 1. Recommended baseline investigations.

Blood tests

- Full blood count
- Inflammatory markers – e.g. ESR, CRP, PV
- Renal function
- Liver function
- Calcium and alkaline phosphatase
- Rheumatoid factor
- Thyroid function
- Glucose
- Protein electrophoresis
- Creatinine kinase

Urine tests

- Urine dip stick – e.g. glucose, blood, protein, nitrites
- Bence Jones protein

Specialist imaging such as musculoskeletal ultrasound of the shoulders and hips is now used in some hospitals to aid the diagnosis of rheumatic disease; however, its role in primary care remains to be defined. In some patients a chest X-ray is indicated if respiratory pathology is suspected or if the patient has prominent systemic symptoms.

TABLE 1. Conditions that can mimic PMR.

Category	Example
Inflammatory rheumatological disorders	Rheumatoid arthritis Giant cell arteritis Spondyloarthropathy Crystal arthropathy
Non-inflammatory rheumatological disorders	Osteoarthritis Shoulder pathology (e.g. frozen shoulder, rotator cuff disease) Fibromyalgia
Infection	Bacterial endocarditis, osteomyelitis, septic arthritis, tuberculosis and other infections
Malignancy	Leukaemia, lymphoma, myeloma Solid tumours (including prostate, renal, lung)
Endocrine	Diabetes Hypo/hyperthyroidism Hypo/hyperparathyroidism
Other disorders	Drug-induced (e.g. statins) Motor neurone disease Parkinson's disease

NB: This list illustrates some conditions to consider when evaluating patients with suspected PMR and is not intended to be exhaustive.

TABLE 2. Diagnosing PMR: the spectrum of classical vs atypical PMR.

	History, examination, investigations	Trial of gluco-corticoids: dose	Response to treatment
A safe diagnosis of PMR in primary care can be made in presence of ALL THREE of these	Classical clinical features	15 mg prednisolone	'Magic', 'miracle', within 3 days
Consider other diagnoses if ANY of these are present (but can be 'atypical PMR')	Atypical features	Need for >15 mg prednisolone to relieve symptoms	Incomplete or delayed response

How to treat and monitor PMR

For most patients with PMR the mainstay of treatment is with glucocorticoids, usually oral prednisolone, although there is limited trial evidence to support the use of injectable glucocorticoids (such as intramuscular methylprednisolone) in patients with mild or localised symptoms. The mechanism of action of glucocorticoids in PMR is not fully understood, but high doses (30 mg prednisolone or more) should not be required. There is no role for the routine use of non-steroidal anti-inflammatory drugs.

The response to the initial glucocorticoid treatment could be viewed as an (admittedly imperfect) diagnostic test for PMR. This 'test' is most specific for PMR as patients feel completely better ('magic' or 'miracle' effects) after 3 days of 15 mg prednisolone. Sensitivity of the 'trial of steroids' is probably improved, at the cost of some loss in specificity, if patients are allowed longer (1–2 weeks) to achieve a 70% reduction in symptom scores, or if they are given higher doses (e.g. 20–25 mg prednisolone).

After the initial response, the glucocorticoid dose is tapered gradually. The average length of treatment in hospital-based cohorts is around 2 years but with wide variation. There is little evidence to help decide

how to taper the dose. Some patients need a much slower taper than others, and some patients develop significant glucocorticoid toxicity. To reduce the risks of treatment, it is usually recommended to try the quicker taper first, but to slow this taper down if need be to keep the PMR symptoms under control. Individualised treatment and shared decision-making should be the rule rather than the exception.
The aim of PMR treatment is to achieve acceptable control of PMR symptoms while minimising the risks and side-effects of treatment. Therefore, if a patient feels their PMR is well controlled, there is no need to re-check inflammatory markers before reducing the dose. A transient (<1 week) increase in PMR-like symptoms after dose reduction is common and usually manageable if patients are forewarned.

A key role of the GP is to regularly monitor patients, checking for alternative diagnoses and assessing the risks and side-effects of glucocorticoids, which are common in PMR[6] and are a major consideration when making decisions on tapering rates. Risks and side-effects such as weight gain, skin fragility, changes in physical appearance, infections, glaucoma, steroid myopathy, osteoporosis/fracture, avascular necrosis, hypertension, diabetes, psychiatric morbidity, and peptic ulcers should all be considered as appropriate for each individual patient. Consider adding calcium, vitamin D and perhaps bisphosphonate according to local guidelines. It may be wise to monitor blood glucose and blood pressure intermittently. Patients should be offered a 'steroid card' and access to support and information about their condition.

BOX 2. Suggested steroid therapy regimen[4]
(Reproduced with permission from: B Dasgupta and Oxford University Press).

- Daily prednisolone 15 mg for 3 weeks
- Then 12.5 mg for 3 weeks
- Then 10 mg for 4–6 weeks
- Then reduction by 1 mg every 4–8 weeks or alternate day reductions (e.g. 10/7.5 mg alternate days, etc.)

Rheumatologists often see the atypical cases, those with incomplete glucocorticoid response and those with difficulty in stopping glucocorticoids. Some rheumatologists use methotrexate or other drugs but most of the evidence comes from rheumatoid arthritis rather than PMR. If used, methotrexate also requires monitoring for potential toxicity.
Non-pharmacological treatments have not been formally evaluated although many patients self-manage pain and stiffness with heat packs and simple analgesia. Whilst physiotherapy interventions have not yet been formally investigated the maintenance of joint ranges around the shoulders and hips with gentle exercise is prudent and patients anecdotally report improvements in stiffness and pain as well as function. Additional strengthening exercises can be added to a daily programme to maximise general activities of daily living and mobility. Effective physiotherapy exercise can be enhanced by general advice relating to keeping active, optimal posture, diet, the use of heat, minimising the risk of falls, pacing strategies as well as being alert to headaches or other potential related symptoms.

BOX 3. Items to potentially include in a PMR review.

- Discussion around the diagnosis, management, course and prognosis of PMR
- Provide written information on PMR
- Provide written information on GCA, including red flag signs
- Osteoporosis risk assessment
- Blood pressure monitoring
- Diabetes assessment
- Advice on keeping physically active
- Assessment of potential impact of glucocorticoids on comorbid conditions

Patient education forms an essential part of management for patients with PMR. Written information should be provided giving details of the natural history of the condition, along with information on treatment, side effects and 'red flags' (including giant cell arteritis). In addition to our resources for PMR, PMRGCAuk is a registered charity that provides a range of services, including a telephone helpline, for patients and their families.

Do not miss giant cell arteritis

Perhaps 5–10% of patients with PMR are also diagnosed with giant cell arteritis (GCA); in some cases the GCA only appears later.[1] Untreated GCA can result in permanent visual loss or stroke, and as such is a 'must not miss' diagnosis. Tell patients with PMR to look out for headache, scalp tenderness, jaw pain/claudication and visual disturbance. GCA symptoms may need high glucocorticoid doses (usually at least 30–40 mg/day prednisolone) so the risk of steroid-associated side-effects is high. Patients suspected as having GCA should be urgently referred to local specialist services (usually rheumatology or ophthalmology, but this is dependent on local care pathways).

Specialist referral

Many patients with suspected PMR can be safely diagnosed and managed in general practice. Referral is usually indicated for one of two reasons: diagnostic uncertainty and lack of response to primary care treatment.

The British Society for Rheumatology recommends referral in the following situations[4]:

- younger age (usually less than 60 years)
- no shoulder involvement
- lack of inflammatory stiffness
- insidious onset
- normal or very high inflammatory markers
- red flag features (e.g. prominent systemic features, weight loss, night pain, neurological signs)
- suspicion of co-existing giant cell arteritis
- poor or incomplete response to glucocorticoids
- difficulty reducing steroids dose
- recurrent relapse
- contraindication to glucocorticoid treatment.
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References

1. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. Ann Rheum Dis 2006 Aug;65(8):1093-8.
2. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum 2011 Mar;63(3):633-9.
3. Helliwell T, Hider S, Mallen S. Polymyalgia rheumatica: Diagnosis, prescribing and monitoring in primary care. Br J General Prac 2013 May;63(610):e361-6.

4. Dasgupta B, Borg FA, Hassan N, Barraclough K, Bourke B, Fulcher J, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatica. Rheumatology (Oxford) 2010 Jan;49(1):186-90.
5. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2012 Apr;71(4):484-92.
6. Mazzantini M, Torre C, Miccoli M, Baggiani A, Talarico R, Bombardieri S, et al. Adverse events during longterm low-dose glucocorticoid treatment of polymyalgia rheumatica: a retrospective study. J Rheumatol 2012 Mar;39(3):552-7.

Further reading and useful resources

- Helliwell T, Hider S, Barraclough K, Dasgupta B, Mallen C. Diagnosis and management of polymyalgia rheumatica. Br J Gen Prac 2012 May;62(598):275-26.
- Barraclough K, Mallen C, Helliwell T, Hider S, Dasgupta K. Diagnosis and management of giant cell arteritis. Br J Gen Prac 2012 Jun;62(599):329-30.
- Mackie S, Mallen C. Polymyalgia rheumatica. BMJ 2013 Dec;347:f6937.

Patient resources

- www.pmrgca.co.uk
- Polymyalgia rheumatica (PMR)
  - See more at: http://www.arthritisresearchuk.org/health-professionals-and-students/reports/hands-on/hands-on-spring-2014.aspx#sthash.YbtEWd1l.dpuf